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Technical Aspects of Laparoscopic Liver Resection. An Experimental Study

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Abstract
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Various techniques are used to transect the liver. With increase in laparoscopic liver resections (LLR), it is of even more interest to develop surgical techniques to minimize bleeding and the risk for gas embolism during transection. Instrument like argon enhanced coagulator provides good hemostasis but increases the danger of gas embolism. The CO_2 pneumoperitoneum that is routinely used in most types of laparoscopic surgery can be modified by the use of different gas pressure. It can be assumed that different pressure influences bleeding but also the risk for gas embolism.

In presented porcine studies, three instrumental combinations have been studied. In study I sixteen piglets were randomized to LLR with either the cavitron ultrasonic aspirator (CUSA™) in combination with vessels sealing system (Ligasure™) or with CUSA™ and ultrascision scissors (Autosonix™), with the endpoints of intra-operative bleeding and gas embolism. In study IV sixteen piglets were randomized to LLR either with staple device (Endo-GIA™) or the Ligasure™ - CUSA™ combination with same primary endpoints and additionally secondary endpoints of effect on gas-exchange, systemic- and pulmonary hemodynamic.

Focusing on intra-abdominal pressure (IAP) in study II, sixteen piglets were randomized to LLR with an IAP of either 8 or 16 mmHg. Primary endpoints were bleeding and gas embolism and secondary endpoints, effect on gas-exchange, systemic- and pulmonary hemodynamic.

In study III effect of argon gas was tested during LLR. Sixteen piglets were randomized to either argon pneumoperitoneum or CO_2 pneumoperitoneum. Primary endpoints were effect on gas-exchange, systemic- and pulmonary hemodynamic.

In presented studies, we tested efficacy and safety of different techniques for LLR. CUSA™ can be used in combination with either Ligasure™ or Autosonix™. However, Ligasure™ reduces the amount of bleeding. The recent introduction of staplers seems promising with a further reduction in bleeding, gas embolism, and operating time. The IAP influences both the amount of bleeding as well as gas embolism. It seems reasonable to use a higher IAP to decrease bleeding with caution and with close monitoring for gas embolism. Argon gas embolism gives more extensive effect on gas-exchange and hemodynamic and should probably be avoided in this type of surgery.

Keywords: Gas embolism, laparoscopy, liver resection, pneumoperitoneum, carbon dioxide, argon, bleeding, stapling device

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Það kann að virðast klisjukennt,
þó kyrrir ýmsa bresti;
að mannvirðing og æðri mennt
er mæta góð í nesti.

-Hrefna Rún-

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I **Eiriksson K**, Fors D, Rubertsson S, Arvidsson D. Laparoscopic left lobe liver resection in a porcine model: a study of the efficacy and safety of different surgical techniques. *Surg Endosc*. 2009;23:1038-42.

II **Eiriksson K**, Fors D, Rubertsson S, Arvidsson D. High intra-abdominal pressure during experimental laparoscopic liver resection reduces bleeding but increases the risk of gas embolism. *Br J Surg*. 2011;98:845-52.

III **Eiriksson K**, Fors D, Rubertsson S, Arvidsson D. Is there a difference between carbon dioxide and argon gas embolisms in laparoscopic liver resection? *Submitted manuscript.* 2012.

IV **Eiriksson K**, Fors D, Waage A, Rubertsson S, Arvidsson D. Faster and safer resection with stapler device: RCT of laparoscopic liver resection in a porcine model. *Submitted manuscript*. 2012.

Additional publications (papers) during my PhD studies, which are not included in this thesis:

I Fors, D., **Eiriksson, K**., Arvidsson, D., Rubertsson, S.
Gas embolism during experimental laparoscopic liver resection–frequency and severity. *Br J Anaesth.* 2010 Sep;105(3):282-8.

II Fors, D., **Eiriksson, K**., Arvidsson, D., Rubertsson, S.
Elevated PEEP without effect upon gas embolism frequency or severity in experimental laparoscopic liver resection. *In press, Br J Anaesth.*

III Fors, D., **Eiriksson, K**., Arvidsson, D., Rubertsson, S.
High Frequency Ventilation shortened the duration of gas embolisation during experimental laparoscopic liver resection. *Submitted manuscript*.

Contents

Abbreviations

AEC	Argon-enhanced coagulation
AP	Arterial blood pressure
ASA score	American Society of Anesthesiologists score
a.u.	Arbitrary units
AVC	After vein cut
BVC	Before vein cut
CO	Cardiac output
CI	Confidence interval
CVP	Central venous pressure
HCC	Hepatocellular cancer
HR	Heart rate
IAP	Intra-abdominal pressure
ICP	Intracranial pressure
IVC	Inferior vena cava
LLR	Laparoscopic liver resection
MAP	Mean arterial pressure
MPAP	Mean pulmonary arterial pressure
$PaCO_2$	Partial pressure of CO_2
PaO_2	Partial pressure of O_2
PAP	Pulmonary arterial pressure
PCWP	Pulmonary wedge pressure
PPP	Post pneumoperitoneum (if with number=minutes)
PVR	Pulmonary vascular resistance
RCT	Randomized controlled trial
SSPO	Steady state pre-operative
SSPP	Steady state at pneumoperitoneum
SV	Stroke volume
SVI	Stroke volume index
SVR	Systemic vascular resistance
TEE	Trans-esophageal echocardiogram

Introduction

The unique ability of the liver to regenerate after resection, its functional reserves, and the knowledge about its anatomy form the basis for innovative approaches to liver surgery. The enormous steps forward in the surgical technology, anesthetics, oncologic treatment, and imaging in recent decades have played a central role. Because of this, the indications for liver resection have changed and increased over time. Patients with both benign and malignant disease are considered, and even patients with a large tumor burden are now considered candidates for surgery while those with limited extra-hepatic tumor growth are not excluded[1-3].

With the fast-growing application of laparoscopic techniques for surgery in general, the new techniques and instruments require investigation regarding their efficacy, effectiveness, and safety. The increased interest in using a laparoscopic approach in liver surgery has taken time to develop first and foremost because of the complexity of the operations and the danger of major complications. These factors have led to a thorough look at the techniques and instruments with regard to safety and efficacy[4-10]. Although some centers perform more than 50% of liver surgeries using a laparoscopic approach[5, 11, 12], the field is still a considerable distance away from seeing all hepatobiliary surgical units apply the technique.

With the help of an animal model, the studies presented here were conducted to contribute knowledge about the safety and efficacy of defined instruments in liver surgery and the appropriate pressure level of pneumoperitoneum.

Anatomy and physiology

Human liver

One of the first recorded tales about the liver comes from the legend of Prometheus, written by Hesiod (750–700 BCE). Prometheus was chained to a rock because he stole fire from Zeus and gave it to humankind. Zeus sent an eagle to eat Prometheus' liver, and the bird returned every day to eat because the liver regenerated overnight[13]. An Alexandrian physician Herophilus (330–280 BCE) was one of the first to describe the anatomy of the liver, although no documents exist directly from him. The Greek physician Galen cited the work of Herophilus in 130–200 CE when he identified the liver as the source of blood. Monographs of Francis Glisson from 1654 form one of the first accredited reports of the anatomy of the liver[14]. Glisson's work was forgotten for over 200 years. Later, in the late 19th century, several authors published studies on liver anatomy, all built on Glisson's writings[14]. In 1888, Hugo Rex from Germany and in 1897, James Cantlie from Liverpool, England, challenged the accepted anatomic division of the liver. They suggested a division line drawn from the top of the gallbladder and back towards the vena cava[13]. Largely because of the work of the French surgeon and anatomist Claude Couinaud, the anatomy of this otherwise complicated organ has become clearer[15]. Through his work making casts of the vascular and biliary structures of the liver, he studied the anatomy and defined it from the vascular structures serving each area of the organ. His suggestion of dividing the liver into eight segments according to the portal vein and venous branching is the segment definition most liver surgeons use today (Figures 1)[14, 16, 17]. As the largest organ in the human body, the liver has four

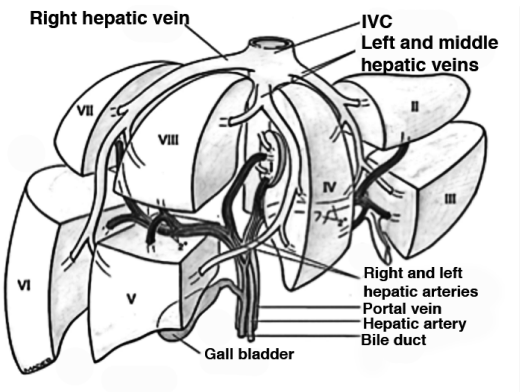

Figure 1. Couinaud's classification of segments.

lobes, the right, left, quadrate, and caudate lobes. The liver weighs 1200–1600 g in an adult, is heavier in men than in women, and constitutes roughly 1/40 of the total body weight. Positioned in the right upper quadrant of the abdomen, the liver is attached with peritoneal reflections, referred to as ligamentous attachments. Up to 80% of the oxygen to the liver is delivered via the portal vein arising from the superior mesenteric and splenic veins. The remaining 20% of oxygen is transported via the hepatic artery[18]. Three veins—the right, middle, and left liver veins—drain the liver right into the inferior vena cava (IVC). The vasculobiliary system is separate at each site, without any connection between the left and right.

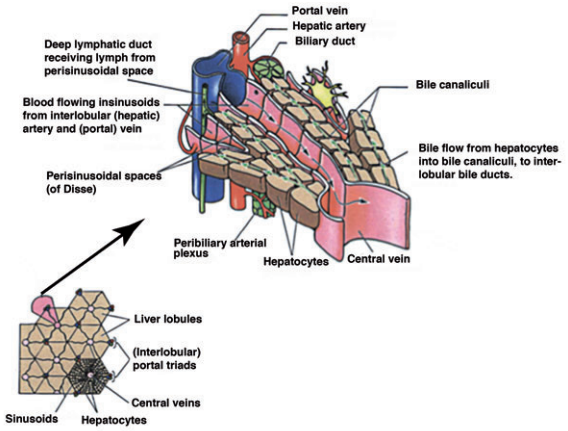

Figure 2. A hepatic liver "lobule" illustrates the components of the interlobular portal triad and the positioning of the sinusoids and bile canaliculi. The enlarged view of the surface of a block of parenchyma removed from the liver demonstrates the hexagonal pattern of "lobules" and the place of the detailed figure within that pattern.

The main structural component of the liver is the liver cell or hepatocyte. These epithelial cells are arranged in units called liver lobules, a polygonal mass of tissue that is not separated by any other tissue. Each lobule contains 3–6 portal triads at the corners of the lobule. Every portal triad contains venules (from the portal vein), an arteriole (from the hepatic artery), and a duct (from the bile duct). Some of the liver sinusoids are lined with a single layer of hepatocytes so each hepatocyte has at least two sinusoidal surfaces. In part, there are double layers of hepatocytes where the space between the two layers makes the bile canaliculi that drain to the bile duct in the portal triad (Figure 2).

The liver is an important storage area for carbohydrate metabolism and also contributes to body fat metabolism. In addition, the liver synthesizes almost all lipoproteins, which are needed for the body, cholesterol, and phospholipids.

Another function is detoxification, and the liver is responsible for the metabolism and excretion of hormones and other endogenous regulators. This organ is also vital for protein metabolism and synthesis of proteins and facilitates excretion of lipid-soluble waste products in the bile[19].

The complicated physiology of the liver is beyond the scope of this text and will not be discussed in more detail. One relevant observation, however, is

that for the liver to maintain its function, good blood circulation to it is vital, and the liver in fact receives 30% of the cardiac output (CO).

Porcine liver

The porcine liver is similar to the human liver the porcine liver is about 3% of the body weight in newborn piglets and becomes 1.5% of the body weight in a full-grown animal, compared to 2.5% of body weight in an adult human[20]. Approximately 25% of the CO is included in the total hepatic

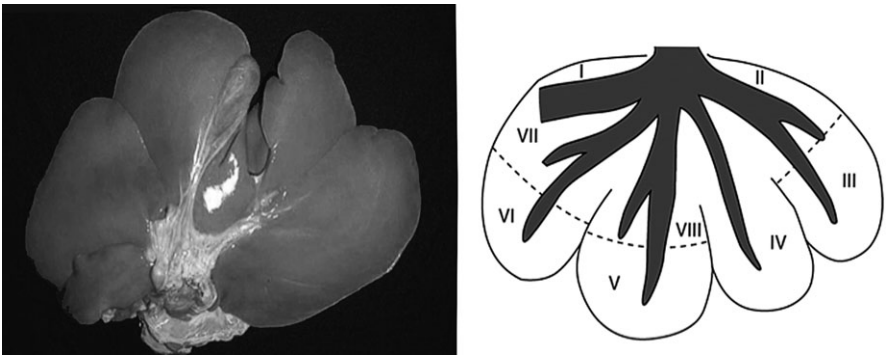

Figure 3. Left) Porcine liver, inferior view. Three lobes are identifiable, and the middle one with the deep fissure is beside the gall bladder. Right) Illustration of the venous drainage of a porcine liver. Four veins drain into the IVC, which is buried in the parenchyma of the caudate lobe

blood flow.
The porcine liver is segmented like the human liver[21]. It has four main lobes: the right lateral, median, left lateral, and caudate lobes. Deep interlobular fissures divide these lobes. The median lobe is divided into two portions sometimes referred to as the left medial and right medial (Figure 3). Unlike the human liver, the pig liver has a bigger left than right lateral lobe and the IVC is buried in the caudate lobe. The left lobe is the biggest if the median lobe is counted as two lobes. The porcine liver is thinner and has generally less volume compared to the human liver.
The biliary, venous, and arterial systems are similar between the species. The veins in the porcine liver are strikingly fragile, and the same can be said about the IVC, which makes a proper right hemi-hepatectomy difficult to perform. In studies discussed in this thesis, we have performed resection of the left lateral lobe. In the left lateral lobe, the portal vein and artery arrive in the anterior edge of the lobe, and the vein enters just before the median part of the lobe.

The histology of the porcine liver is similar to that of the human although the porcine lobules have connective tissue between each other, which the human lobules do not. The relevance of this difference is not clear.
The metabolic function of the porcine liver is very similar to that of the human liver, even more similar than in many primates[20].

Liver surgery

Historical facts

In the 19th century, two fundamental concepts changed the possibilities for successful surgery: anesthesia and aseptic technique. Before this time, anecdotal evidence exists of liver treatment with some resection in relation to injury but not of planned liver resection[13]. In 1886, Lius performed the first elective liver resection when he removed a left lobe adenoma from a 73-year-old woman, but the patient died postoperatively from a hemorrhage[22]. Carl Von Langenbuch reported the first successful resection in 1888[13]. Bleeding from the liver has been the center of attention and has led to development of a wide range of methods through the years in the attempts to minimize bleeding during liver surgery. In 1896, Michael Kousnetzoff and Jules Pensky recommended the use of a mattress suture over the resection line to control bleeding, and in 1908, James Hogarth Pringle introduced the Pringle's maneuver for reducing inflow into the liver by compressing the portal inflow vessels and thereby minimizing the bleeding[23]. Sadly, all of the eight patients Pringle reported died during or after the surgery[24]. Interest in the anatomy of the liver, however, did place liver surgery on the right track. In the early 20th century, Walter Wendell in Germany and Hans Von Haberer in Austria performed the first resection along the Rex-Cantile line, the avascular plane between the right and left liver, along the middle vein[13]. Jean Louis Lortat-Jacob, in Paris, performed the first true right anatomical resection in 1952, a single case, in which his assistant had identified a tumor in the right liver lobe of a 42-year-old woman. The patient was discharged from the hospital 1 month after the surgery[24].

One reflection of how the hepatic surgeons tried to improve safety is the development of the Pringle and other maneuvers on the extra-hepatic vasculature, and in recent decades, of high-tech instruments used in combination or not with other methods to reduce bleeding during division of the parenchyma[22, 23].

The laparoscopic era of liver surgery started with the use of a laparoscopic method for de-roofing of non-parasitic hepatic cysts in 1989, published by

Fabiani et al[25]
Since the first laparoscopic liver resections (LLRs), performed by Reich et al in 1991[26] and Gagner et al in 1992[27], the increase in laparoscopic liver surgery frequency has been steep. The resections performed by Reich and co-workers were of one focal nodular hyperplasia and of a hemangioma. Gagner and colleagues removed an adenoma from the left liver. All of these resections were minor and non-anatomic and with restricted removal of liver parenchyma. At first, the indications for LLR were lesions in the left liver and on the anterior right liver. The first segment resection was published by Azagra et al where they described a left lateral segmentectomy[28]. Some authors have suggested that LLR expands the indications for hepatectomy in cirrhotic patients with hepatocellular carcinoma (HCC)[29].
The most performed resections are for peripheral lesions, especially on the left side of the liver[5-7, 10, 30-34]. Some authors consider the laparoscopic approach as a routine technique for bisegmental resections of segments II and III [35]. A case report from Costi et al[36] in 2002 showed that lesions in the posterior segments of the liver could also be removed with a laparoscopic approach. The posteriosuperior segments pose a challenge compared to the anterior segments; however, with appropriate skills, techniques, positioning, and equipment, resection is feasible and safe[37]. In some centers, the indications for a laparoscopic approach are similar to those for an open approach[38].
In the beginning, a laparoscopic technique was used only for benign lesions[39], but later its use was extended to malignant tumors, as well[5, 7, 31, 34, 40].
Currently, several centers perform major liver resections with a laparoscopic approach[4, 5, 11, 41-43], and in some centers, the laparoscopic method constitutes $\geq$50% of all liver resections[5, 11, 12]. Laparoscopic resections have also been used to harvest donor liver[44], with the left liver for adult-to-child transplantation and also larger resections for adult-to-adult transplantation. Complex biliary or vascular reconstruction and very big tumors have been accepted as contraindications for laparoscopic resection[45].

Access and efficacy of laparoscopy

No matter which technique is used to divide the liver, access to the surgical field is the most important factor for performing a safe surgery. Jean Louis Lortat-Jacob and co-workers used a laparo-thoracotomy approach in the first true anatomical resection, which Robert repeated in 1952. Other surgeons performing liver surgery soon adopted this approach[24]. Later, the use of an upper abdomen transverse incision or an inverted L-, J-, or Mercedes incision was preferred with or without a thoracotomy[46, 47]. Now with laparoscopy, and a few small incisions, the same resections are performed.

The newest method to access the liver in the minimally invasive field is the single port approach[48], a technique outside the scope of this thesis and therefore not discussed in detail.

Conversion rates have been reported from 2.3–15%[38, 43, 45, 49-55]. Although conversion is seen as a change of operation plans rather than failure, it is a sign of problems during the operation that can lead to more blood transfusion, longer operations, prolonged wound healing, a longer hospital stay, and more postoperative morbidity[56]. The most frequent reasons for conversion have been unmanageable bleeding, adhesions, unreachable location, deprived exposure, close proximity to major vessels, doubt about tumor margins, gross positive tumor margins, and lack of advancement. The weight of the patient is a risk factor for conversion, and previous liver surgery possibly increases the conversion rate somewhat[56, 57]. The experience of the surgical team is important, and centers of excellence do not have conversion rates higher than 5%[40, 45].

Compared to open surgery, the laparoscopic approach in general can lead to less postoperative pain and reduced need for analgesics, decreased bleeding, less danger of postoperative hernia, reduced infection rates, earlier discharge from the hospital, less immunological stress with possible better oncologic outcome, fewer adhesions, and better cosmetic results[49, 51, 53, 54, 58-63]. Although the surgical stress is less in laparoscopic surgery, there is still surgical stress involved[64]. Because the majority of liver resections are performed for removal of malignancy, the possible positive oncologic effects are important, as is the reduced formation of adhesions. Malignancy can lead to repeated resections for patients with heavy tumor loads and recurrent disease[38, 65]. A study by Burpee et al[66] on a porcine model showed lower tumor necrosing factor (a non-specific marker of inflammatory processes) and lower interleukin-6 (a sensitive marker of tissue damage) after LLR than after a similar resection done by an open approach. In the same study, they looked at the development of adhesions 6 weeks after the operation and found that adhesions after a laparoscopic approach were fewer, thinner, less vascularized, and less persistent. A clinical study of laparoscopic re-resections did show more bleeding and more need for blood transfusion after previous open liver surgery compared to previous laparoscopic liver surgery[57].

Questions have been raised regarding the safety of a laparoscopic approach in cancer in general, specifically about insufficient margins of resection, increased local recurrence and extra-hepatic recurrence, inadequate lymph node clearance, increased port site metastases, and poorer long-term outcome[67]. Studies looking at operations with a major focus on lymph node clearance have not shown inferior outcomes with the use of laparoscopy[53]. Intermediate and long-term oncologic outcome in individual reports are promising[12, 38].

Eight meta-analyses of laparoscopic versus open resections have been published, the first in 2007. Five of these looked at both benign and malignant tumor resections[49, 52, 54, 68, 69], and three included studies of resection in HCC[51, 70, 71].

A meta-analysis of 26 comparative studies, with 1678 patients undergoing laparoscopic (717 patients) and open (961 patients) liver resections, found no difference between resection free margins and an increase in <1 cm resection margin in open operations in the studies that reported this. Recurrence was similar for laparoscopic and open resections for HCC, but results were not available for colorectal cancer metastases because of trial heterogeneity. The laparoscopic and open methods did not differ regarding extra-hepatic recurrence of HCC, and there was a trend toward increased overall survival in patients operated on with a laparoscopic approach[49]. Another, more recent meta-analysis of 10 comparative studies (case-control and retrospective) on laparoscopic versus open liver resection for HCC found no difference between groups in regards to surgical margin, positive margin rate, or tumor recurrence[51]. It has to be noted that no randomised controlled trial (RCT) has been done to compare laparoscopic and open surgery for hepatic resections and that there is a possible selection bias in the studies involved in these meta-analyses.

Dividing the liver parenchyma

The major problem with liver transection is the bleeding. Two aspects of bleeding are important: first, the intra-operative danger of hypovolemia with possible catastrophic hemodynamic results, and second, the need for blood transfusion, which can lead to an inferior outcome both with increased morbidity and poorer survival from underlying malignant disease[72, 73]. Various methods have been suggested to minimize the blood flow in the liver regardless of the choice of instruments for dividing the liver tissue. The Pringle's maneuver is widely used, and discussion is ongoing about the correct use of this maneuver to keep ischemic injuries to a minimum. In a 2009 Cochrane review that included 10 trials with 657 patients, the conclusion was that it was better to use Pringle's maneuver intermittently instead of continuously in patients with compromised liver function[74]. The authors found no difference between the use of Pringle's maneuver and hepatic vascular occlusion regarding outcomes. A meta-analysis had earlier shown no difference in outcome between patients who had portal triad clamping and those who did not, and the authors concluded that portal triad clamping did not offer any benefit in hepatic resection[75]. A major factor in significantly reducing bleeding is the use of low central venous pressure (CVP)[76-80] during hepatic resection, which is established with fluid restriction pre-operatively to result in a

CVP between 0 and 5 mmHg. The only RCT showed reduced bleeding by 62% in the group with low CVP[80].
The use of hypothermia to protect the liver tissue from longstanding ischemia and ex situ resections has been reported[24], but discussion of those methods is beyond the scope of this thesis.
Numerous types of clamps have been produced with the aim of reducing bleeding from the parenchyma[24, 46, 81]. Lin and co-workers promoted the use of the "finger fracture" technique in 1958[82], the use of the surgeon's finger to fracture the hepatic tissue, exposing the vascular structures within the liver for subsequent closure with ligature or electrocautery. Although not a perfect technique, the majority of hepatobiliary surgeons adopted it, and it is still widely used. In 1953, Quattlebaum described three cases in which he used the handle of a scalpel for dissecting the liver and achieved the same effect as with the finger fracture method[47]. The search for a better division technique continued from the 1950s and is ongoing. Various instruments and techniques have been tried and described: the liquid nitrogen knife in 1955, liver crush clamp in 1974, electrocautery in 1978, microwave tissue coagulator in 1979, laser in 1980, water jet in 1982, UltraCision aspiration dissector in 1984, bipolar electrocautery in 1993, staples in 2006, ultrasonic scissors in 2000, vessel sealing system (Ligasure®) in 2001, bipolar electrocautery with saline irrigation in 2001, radiofrequency ablation (Habib™) in 2002, floating ball cautery in 2004 and saline-linked radiofrequency dissecting sealer (TissueLink™) in 2005[24, 83-93]. Views differ on each of these techniques; some have been adapted for use in liver surgery today, and others have not been widely used. Several instruments are commercially available for the division of the liver parenchyma[33, 94-97].
The increasing volume of LLRs has contributed to faster evolution of instruments for the transection of the liver parenchyma. In this thesis, the focus is on ultrasonic scissors (Autosonix™), a vessel sealing system (Ligasure®), an ultrasonic aspiration dissector (CUSA™), and staples (Endo-GIA™ Universal).

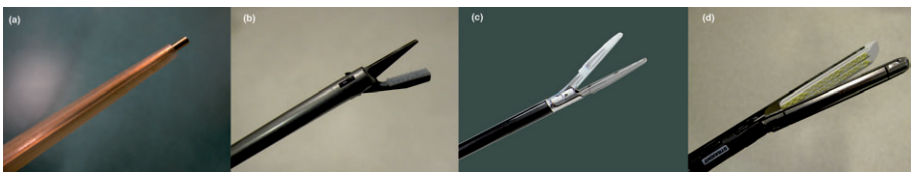

Figure 4. (a) CUSA™, (b) Ultra shears™, (c) Ligasure™ and (d) Endo-GIA™, vascular stapler.

Instruments in focus–technical aspects

Ultrasonic aspiration dissector, ultrasonic scalpel, or Cavitron Ultrasonic Surgical Aspirator (CUSA™)

The interaction between ultrasound and living tissue is complex. It depends on the type of tissue, its condition, the mode of ultrasound application, and several acoustic parameters, including the frequency, tip area, tip shape, amplitude, and the resulting pressures or intensities. Three modes are considered for the interaction between ultrasound and living tissue: 1) thermal, 2) cavitational, and 3) non-cavitational or mechanical. A study on a porcine model defined the strength of a given tissue as ∂ and showed it to be a good indicator of ultrasonic aspirator performance in a given tissue. The brain had the lowest (0.01 MPa) and the aorta the highest (1.34 MPa) strength, and the liver lies in between with ∂=0.25 MPa[98]. When a tissue is relatively mostly composed of collagen and/or elastin, the strength increases, and the ultrasonic aspirator is less suitable for dividing that tissue. Organ capsules, healthy skin, tendons, and vessel structures are examples of tissue that fragments poorly with the ultrasonic aspirator.
The Cavitron Ultrasonic Surgical Aspirator (CUSA™) is an ultrasonically powered aspirator that selectively fragments and aspirates parenchymal tissue while sparing vascular and ductal structures. The movement of the tip can range from 20–60 MHz. The fragmented tissue is aspirated via the hollow tip of the instrument. An irrigation fluid (saline) flows in at about 1 drop/s=50 µL/s=3 mL/min. The purpose of the irrigation is both to cool the tip of the instrument and to blend in the fragmented tissue to avoid clogging of the instrumental tip and the efferent suction line. The suction of the instrument is set to 90% of maximal suction effect. The function of the suction is to remove fragmented tissue, and the suction plays a role in the defragmentation of the tissue by sucking the tissue in toward the moving tip of the instrument. Without suction, an excessive pressure is necessary to acquire an effect similar to that of suction[98]. In the present studies, a CUSA System 200™ (Valleylab) was used (Figure 4).

Ultrasonic scissors (Autosonix™ with 5 mm Ultra Shears™)

The Autosonix™ system includes a generator, transducer, and hand instrument with a titanium probe. The generator produces a 55.5-kHz electrical signal and feeds that signal to piezoelectric crystals in the transducer. The resulting mechanical vibration releases energy to the tissue. The vibration

amplifies as it transfers the length of the titanium probe, leading to ablation, cauterization, or cutting. The blade's movement range is a distance of 50 to 100 µm, and the lateral spread of energy is about 500 µm. In the presented studies, the energy level of the generator was kept at 2.5, which generates about 75 µm of moving distance for the blade. The higher the level, the faster the instrument divides the tissue, meaning that a poorer coagulation effect is achieved. These shearing forces separate tissue and heat the surrounding tissue to a level that permits coagulation and sealing of blood vessels without the burning associated with electrocautery. The coagulation effect is achieved with the denaturizing of proteins by destruction of hydrogen bonds in the proteins and heat formation. According to the manufacturer, when placed in a liquid, the vibrating tip causes microscopic bubbles to grow and then collapse with great energy intensity, resulting in the liquefaction or fragmentation of tissue directly in front of the probe. The mouth of the instrument contains one site with a tagged surface for grip of the tissue, and the other is the slightly angled blade that transfers the energy to the tissue. (Figure 4)

Vessel sealing system (Ligasure™)

The Ligasure™ instrument is a vessel sealing system with a generator that gives 4.0 A as the maximal electrical current to the tissue. The instrument measures the impedance in the tissue (200 times per second) and in that way provides confirmation of the sealing of the vessels. The initial impedance determines the choice of electrical current that is delivered. This process is automatic. The generator emits a sound when sufficient sealing is achieved. For the peak activation cycle, electromotive force is 180 V. An average seal cycle is 5 to 8 s. The choice of instrument size in our studies was 5 mm Ligasure™.

The instrument is built up with a U-shaped peripheral area in both parts of the mouth that delivers the current and measures the impedance. In the middle of the mouth of the instrument is a knife blade that is available for dividing the tissue. Division is applicable only within the sealed area, which is important if the tip of the instrument is placed on the edge of a bigger vessel and activated. In these circumstances, bleeding from the vessel might be expected but is not necessarily the case with Ligasure™. (Figure 4)

Staples (Endo-GIA™ Universal Stapling System)

The staples used in study IV were white cartilage with each titanium staple 2.5 mm high before firing. After firing, the staple was 1 mm in height with a

B-shape. Three staple lines are on each side of the dividing knife that is built into the instrument. (Figure 4)

Pneumoperitoneum

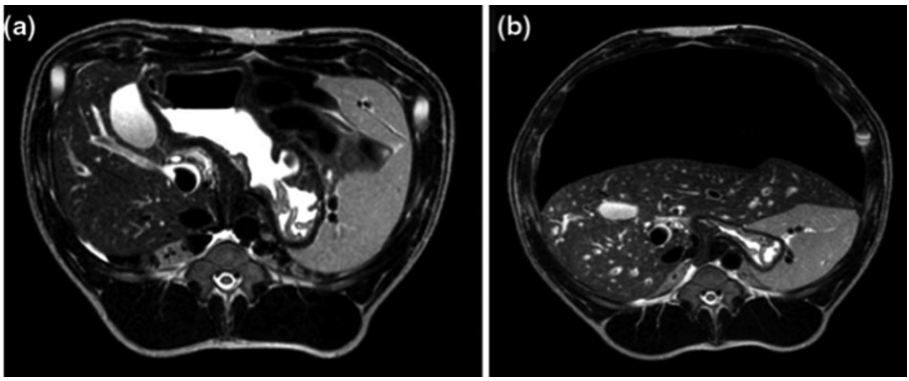

Figure 5. MRI of a pig at (a) no pneumoperitoneum and at (b) 14 mmHg CO_2 pneumoperitoneum (published with permission from authors, F. M. Sánchez-Margallo et al (108)).

Performing a laparoscopic examination and surgery requires making sufficient space for viewing the target tissue. To acquire an adequate overview, gas pneumoperitoneum, abdominal wall lift (isobaric exposure techniques), or both[99] is required. The pneumoperitoneum is a complex and dynamic environment with potential to alter the patient's mechanical, physiologic, and immunological condition and has not been used without concerns in the surgical community[100]. The effect of laparoscopy upon pulmonary and hemodynamic changes is a matter of debate with a degree of disagreement found in the literature[101-105](see Appendix A).
Some major aspects of pneumoperitoneum are discussed here. Three main factors are associated with changes in hemodynamic and respiratory functions: intra-abdominal pressure (IAP), biochemical/physical effects from the gas, and the position of the patient.

Pressure

The choice of IAP level is crucial in terms of the effects on the circulatory and respiratory function of the patient. Published results conflict regarding

the effect of pneumoperitoneum on cardiovascular and respiratory parameters[101, 102, 104-107]. Pneumoperitoneum leads to displacement of the diaphragm, affecting the respiratory pressure regardless of gas type[108]. Lung compliance is reduced[109], the functional residual capacity is reduced, and there is less lung volume and less alveolar ventilation with increased dead space and shunting. The IAP compresses the IVC and reduces the venous return from the lower extremities. Anatomy of organs like the liver changes as a result of the pressure, at least at 14 mmHg[108] (Figure 5). Despite these changes, results from one animal study describe no change in hepatic tissue blood flow between 4 and 15 mmHg although a pressure up to 20 mmHg does reduce hepatic tissue blood flow[110]. In contrast, Takagi[111] showed a significant decrease in portal flow by IAP of just 10 mmHg in a porcine model.

The effect of IAP on hemodynamics depends on (a) intravascular status, (b) baseline hemodynamic status, and (c) the magnitude of pressure. In hypervolemia, the IAP increases the preload and CO; however, in normovolemia and hypovolemia, the IAP reduces the preload with a decrease in CO[104, 112]. Most healthy patients show minimal cardiovascular changes during pneumoperitoneum, but cardiopulmonarily challenged patients (American society of anesthesiologists (ASA) score > II) will show symptoms at an IAP of 15 mmHg including raised blood pressure, increased vascular resistance, and decreased CO[113, 114]. The IAP may also enhance myocardial dysfunction by preload and afterload alterations according to an experimental study by Greim and colleagues[115]. Laparoscopy is not an absolute contraindication for a patient with an ASA score above II; still, a sufficient monitoring is mandatory to avoid intra-operative complications[116]. Junghans et al[117] concluded in their porcine study that an IAP of 16 mmHg had a marked effect on the hemodynamic and respiratory status of the animals regardless of the type of gas used.

Higher IAP (16 mmHg) affects blood flow to the liver and slightly affects renal blood flow[104, 118]. With an even higher pressure of 20 mmHg, the portal blood flow can be reduced by 65% and the hepatic blood flow by 45%[119]. A higher pressure level of CO_2 can lead to lactic acidosis[120], and urine output is reduced by a pressure of 15 mmHg[107]. In animal studies, a pure IAP of >30 mmHg influences hemodynamic status severely and leads to reduced intra-abdominal blood flow with catastrophic consequences[121]. Bleeding from the liver has been shown to minimize with the use of 15 mmHg IAP[122].

A Cochrane review with a focus on post-operative pain looked at the evidence around the choice of low (<11 mmHg) versus high (>11 mmHg) IAP during laparoscopic cholecystectomy in humans. Although the 15 trials in this meta-analysis had a high risk of bias, the authors concluded that lower pressure did lead to less intensive pain, reduced incidence of shoulder pain after the operation, and reduced use of analgesics[123].

Choice of gas

The ideal gas for laparoscopy should be colorless, odorless, non-flammable, not support combustion, inert, soluble in plasma, readily available, cheap, and safe to use for all patients. The gases that have been considered for pneumoperitoneum are air (N_2 78%, O_2 21%, argon 0.9%, and 0.1% others), oxygen (O_2), nitrogen (N_2), nitrous oxide (N_2O), carbon dioxide (CO_2), argon (Ar), and helium (H_2).

Three major concerns must be addressed in the choice of gas for laparoscopy: the danger of combustion, the consequences of possible gas embolism, and the direct physical effect on the hemodynamic and respiratory status of the patient. Air and O_2 are not good choices for laparoscopy because of their oxidizing capacity and the danger of combustion when used with electrocautery. A mixture of possible methane (CH_4) or hydrogen (H) from an open bowel can lead to combustion if the intra-abdominal gas does not suppress combustion. However, the presence of CH_4 and H is rare, and they constitute an insignificant fraction of gas in the abdomen in normal gastrointestinal surgery[124]. Two case reports have described explosions in connection with N_2O pneumoperitoneum. The real role of N_2O in these cases is doubtful, and some authors have suggested reintroduction of N_2O to the surgical field as a replacement for CO_2 on the grounds of the former's limited physical effect on the cardiopulmonary system[124].

Most surgeons prefer CO_2 as the gas of choice for laparoscopic surgery. Although it does not fulfill all the qualities of the ideal gas, no other gas comes nearer the ultimate requirements.

Physical effects of gas

Different gases give different physical effects[117]. The solubility coefficient is the volume of gas that can be dissolved by a unit volume of solvent at a certain pressure and temperature. There is more than one way to describe solubility. For the presented studies, the decision was made to present the solubility as the Ostwald coefficient (L) (volume gas dissolved in volume fluid at 1 atm (760 torr or 101.325 KPa). For measurement of solubility of O_2 and

CO_2, the metabolic factor of these gases must be accounted for[125]. The measurement of the solubility coefficient is outside the scope of this thesis.

Table 1. Ostwald solubility coefficient (L) for gases used for laparoscopic surgery. The numbers are in units mL gas/mL human plasma, at 37 °C and 1 atm pressure. Values in this table are gathered from publication of Langø and colleagues (125).

Gas	O_2	CO_2	Ar	N_2	N_2O	He
L	0.0243	0.582	0.0281	0.0137	0.454	0.0086

As Table 1 shows, the solubility of CO_2 is the greatest of these gas types, and second best is N_2O. Helium has the poorest solubility in human plasma. Because air consists mainly of N_2, the solubility of air is approximately the same as N_2. In relation to the studies presented in this thesis, the Ar gas is about 20 times less soluble than CO_2 in human plasma at 37 °C.
CO_2 has a negative effect on hemodynamic and respiratory status, and the

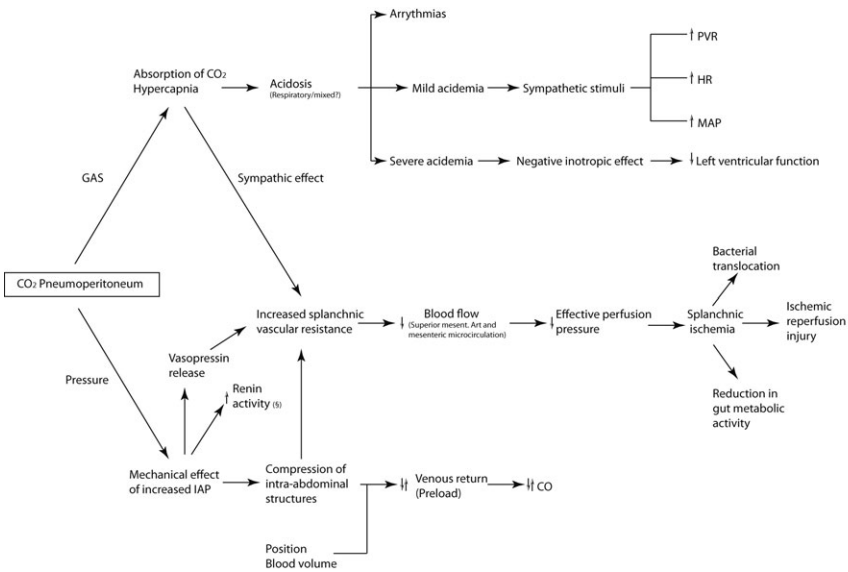

Figure 6. A flow chart of possible effects of carbon dioxide and pressure of pneumoperitoneum. (§) further effects of the renin–angiotensin system are not included.

same applies to Ar; however, H_2, N_2, and N_2O have limited or no effects[107, 117, 126-128]. (Figure 6)
CVP, mean arterial pressure (MAP), and systemic vascular resistance (SVR) are increased by CO_2 pneumoperitoneum[117]. There is also an expected increase in mean pulmonary arterial pressure (MPAP) and pulmonary capillary wedge pressure (PCWP).[105, 129-133] CO_2 is easily absorbed from the peritoneum and excreted by the lungs. In a study by Tan et al[134], a

measurement of absorption of CO_2 from peritoneum in a young healthy female undergoing laparoscopic gynecologic procedures was 42.1 mL/min. There was a 30% increase in elimination of CO_2 via the lungs requiring an increase of 20–30% in the minute ventilation to maintain a normal partial pressure of CO_2 ($PaCO_2$) in blood. Another study revealed a correlation between CO_2 elimination and age and size of children during various laparoscopic procedures[135]. If the ventilation is not adjusted, the CO_2 absorption leads to higher $PaCO_2$ with a direct effect on pH in the blood, something that is not seen in case of pneumoperitoneum by alternate gases at the same IAP level. Thus, it is the physical effect of CO_2 that is reflected without the effect of IAP.[107, 126, 136] The oxygen consumption is unchanged. The increased excretion of CO_2 by lungs during CO_2 pneumoperitoneum is therefore not a result of increased metabolic activity but of the increased absorption from the abdomen[113, 126]. Lister et al[128] showed in an experimental study on pigs that the CO_2 excretion was not linear with the increase in CO_2 pressure in abdomen. The increase in excreted CO_2 rose with an IAP of 0–10 mmHg, but with higher pressure, the excretion did not increase. A possible explanation may be the increased dead space in lungs above an IAP of 10 mmHg[128].

The CO_2 pneumoperitoneum also results in reduced peritoneal pH, and the effect increases with increased IAP[104, 137-139]. The low peritoneal pH was not altered by warm or humidified gas in one experimental study by Wong et al[140]. The nature of the acidosis is controversial; some authors describe it as respiratory or mixed, and others report that there is more of a metabolic component[104, 109, 119, 141-143].

Most patients with normal pulmonary function compensate for this rise in $PaCO_2$ or are helped by the anesthetist with increase in tidal volume to correct the situation[101, 107, 113, 142, 144]. Severe hypercapnia leads to release of catecholamine that influences the cardiovascular system (vasoconstriction) with a rise in MAP and heart rate (HR) and possible arrhythmias. Brady-

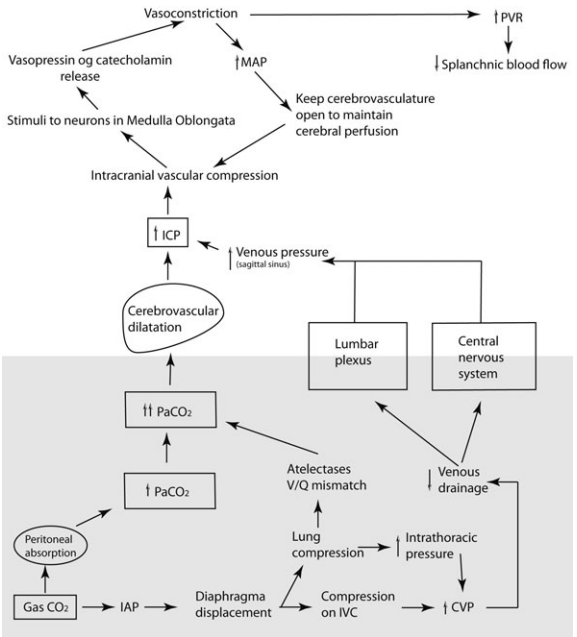

Figure 7. Possible effects of CO_2 pneumoperitoneum on intra-cranial pressure (grey) and the possible hemodynamic effects of increased intra-cranial pressure (white).

cardia is also possible, caused by the peritoneal irritation of the gas, mostly by a CO_2 type of gas. Not all of the patient's symptoms are necessarily because of the gas, however. Situations like pneumothorax, hypoxia, and embolism (both gas and thrombotic) must be kept in mind. In addition, the IAP increases the intracranial pressure (ICP), and with the help of the sympathetic effects of CO_2, this increase can lead to increased sympathetic outflow with increased MAP and SVR as well as decreased HR (the so-called Cushing's reflex, a hypothalamic response to ischemia)[102]. Symptoms of drowsiness, nausea, and vomiting have been associated with the amount of CO_2 used during laparoscopic surgery[145].

Argon gas has been shown to have a more negative effect on liver blood flow than CO_2 or N_2[118]. Effects on respiratory status are not influenced by an Ar pneumoperitoneum although some degree of change in base excess is noted. However, the use of Ar results in a significant reduction in stroke volume (SV) and SV index (SVI)[136]. Compensatory tachycardia and increased SVR (more than seen with CO_2 pneumoperitoneum) are observed but no overall effect on MAP or MPAP[117, 136]. Some authors suggest that Ar may not be as inert as previously thought[136].

The patient's position

With limited options for holding organs away from the surgical field, surgeons make use of gravity by altering the position of the patient. Thus, gynecological, colon, and prostate surgical procedures are usually conducted with the patients in the Trendelenburg position (head down) (see Figure 8) while in surgical procedures on the upper abdominal organs (liver, gallbladder, stomach, spleen), the reversed-Trendelenburg (head up) position is preferred. Other positions like the side position can be preferred, in combination with head-up or head-down. The position on the operating table also influences hemodynamic and respiratory state[117, 146]. Some degree of disagreement persists regarding the respiratory effect of different positions[147].

Figure 8. Old demonstration of a Trendelenburg position.

As a sign of acute volume loading, the Trendelenburg position alone usually leads to increased CVP, CO, MAP, PCWP, and MPAP; however, a fraction of experimental subjects react with decreased or no change at all in MAP[146].

There is a controversy about the Trendelenburg position adding to the CVP rise that was already in place from the IAP[107, 148]. With the reversed-Trendelenburg, the CO decreases in relation to IAP, especially with IAP of 16 mmHg[118]. Junghans et al[118] showed increased SVR with reversed-Trendelenburg that was also correlated with the IAP. Renal and liver blood flow are affected by the head-up position and more so with 16 mmHg IAP.
All animals in our studies were in a reversed-Trendelenburg position of about 5 degrees.

Temperature and humidity of gas

Lowering of the core temperature during surgery is an unwanted event for many reasons. It can increase the infection rate, lead to electrolyte disturbances, impair myocardial function, and influence blood clotting; thus, it can influence mortality and morbidity rates[149]. Controversies exist about the effects of heating the intra-abdominal gas[139, 141, 150-157].
The law of Fick's diffusion is $D=k_B*T/f$, where k_B is the Boltzmann constant ($1.3804688 *10^{-23}$ J/K), T is temperature, and f is the friction coefficient. If we assume that the f is constant, then we will see that a change in the temperature can change the diffusion of CO_2[141]. With lowering the temperature of the gas, the diffusion of CO_2 reduces; however, the core temperature of the patient will fall[141, 152]. Some authors have not found any differences in pH between gas at room temperature (22 °C) or at body temperature (37 °C)[141] while others have[139]. Discussion on this matter is ongoing.
Some results from experimental studies have suggested that heated gas will leave the patient with more adhesions than if the gas is cooler[158]. There are also controversies about increased or decreased pain after laparoscopy with heated gas[151, 153, 159, 160].
The drying effect of the CO_2 gas stream has been suggested as one of the main factors in lowering the core temperature of patients during laparoscopic surgery; thus, humidifying the gas could reduce the problem of hypothermia[149]. Controversies exist about the positive effects and the need for humidifying the gas when used for pneumoperitoneum. Some evidence suggests a positive effect[149, 150, 158] although not all authors agree on this[153]. A recent Cochrane review of 15 studies, published in 2011[161], does not show any benefits of warm gas with or without added humidity.
In the studies presented in this thesis, the gas was at room temperature without added humidity.

Establishing pneumoperitoneum

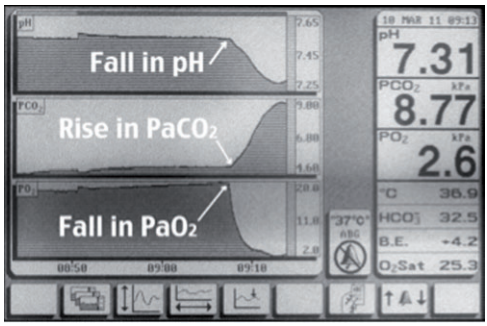

Figure 9. Screen shot of the Paratrend right after the insufflation of CO_2.

The main methods of introducing the gas to the peritoneum are the use of needle (Veress needle) or directly with a trochar (with or without a camera)[162]. An open method (Hassan technique) was introduced to reduce the danger of injury from the sharp Veress needle. Another similar technique (the Scandinavian technique) is also used, through the umbilicus, to guide the way into the abdominal cavity. The frequency of reported injuries is not high[162]; however, a fatal outcome has been described. A meta-analysis with mostly comparative studies that were not randomized was published in 2003[163] with vague and non-conclusive findings. The attitude is now that the surgeon should use whatever technique is most comfortable. However, appropriate respect for the technique is mandatory because the possibility of harm is high.

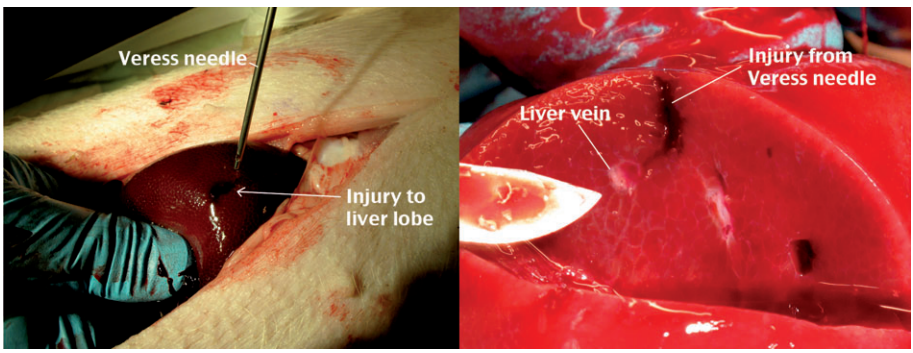

Figure 10. Photos showing injury made by a Veress needle stick into the left medial liver lobe. Injury reaching a branch of the liver vein. Injury with a fatal outcome in this animal.

For establishing the pneumoperitoneum in the presented studies, the Veress needle was used, mainly without complications although one specific operation did not play out as planned. With some problems regarding a distended stomach in the animals, a decision was taken in that case to put the Veress needle further up near the xiphoid process. In the beginning, the pressure was around 3–4 mmHg but suddenly rose to >20 mmHg on the insufflator screen. The needle was retracted because of a suspicion of malplacement. The animal showed a rise in $PaCO_2$ and a serious fall in partial pressure of O_2 (PaO_2) (Figure 9). The blood pressure fell with subsequent asystole. The animal died after inflation of a few hundred milliliters of CO_2 gas. A laparotomy was undertaken to try to find the real reason for the death. By moving the needle further up, the left median lobe of the liver had become the target for the needle. The needle went into the lobe and into a vein so that the insufflated gas went straight into the venous system and killed the animal (Figure 10). Transesophageal ultrasound was not being performed when this happened so no ultrasonic evidence was found showing the embolism in the heart on this animal. However, the AcqKnowledge software program was recording the vital signs (Figure 11).

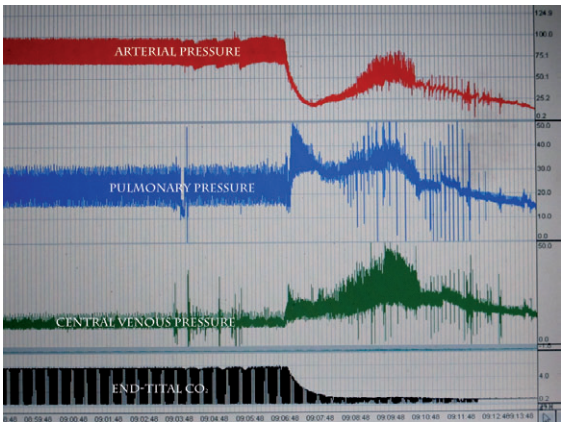

Figure 11. AcqKnowledge registration of AP, PAP, CVP, and end-tidal CO_2.

No other significant insufflation incidents occurred in these experiments.

Complications in focus

Bleeding during laparoscopic liver surgery

As mentioned earlier, the major challenge for the hepatic surgeon is to achieve as little bleeding as possible. With the new improved instruments, this goal is feasible, although large bleeding can occur. The published meta-analyses all agree on the reduction of bleeding by approximately 200 mL with a laparoscopic approach compared to open surgery[49, 52, 54, 55, 68, 69], even

in HCC patients[51, 70, 71]. Selection bias is possible because the tendency has been to select easier cases for the laparoscopic approach and even smaller resections, although that is not the case in all specialized centers[164].
In the case of bleeding during laparoscopic resection, another challenge is to control the ongoing bleeding because the use of pressure as in an open operation is not applicable unless the operation is converted. As stated earlier, this is one of the major reasons for conversion in laparoscopic surgery.
An important tool for safer resection, both regarding clearance of tumor and reduced bleeding, is the laparoscopic ultrasound probe[45, 63]. With visualization of the vasculature, an accidental injury could be reduced. Intra-operative ultrasound was not used in the studies presented here.
Several types of biological and biomechanical sealants and hemostats are commercially available to enhance the effect of the patient coagulation system, e.g., Tachosil® and Duracil®[165]. No sealants or hemostats were used in presented studies.

Gas embolism during laparoscopic liver surgery

The effect of the gas emboli depends on (1) the type of gas (solubility as described earlier), (2) amount of gas, and (3) entrance rate. Studies have shown that the frequency of gas embolism during laparoscopic procedures in

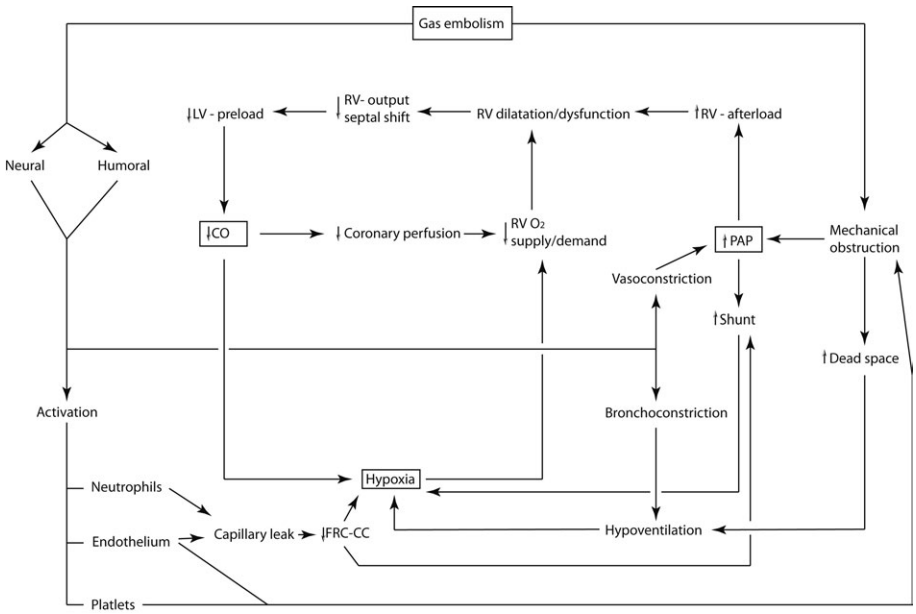

Figure 12 – Possible effects of gas embolism

general is low. Derouin and colleagues[166] reported a detectable gas embolism in 11 of 16 (69%) patients undergoing laparoscopic cholecystectomy. Of these 11 patients, half had embolism during insufflation by a Veress needle. No patient had any clinical effect of this embolism. There are reports in the literature of critical situations and deaths from gas embolism during various laparoscopic procedures [167-181].

The danger of gas embolism during laparoscopic liver surgery has been the center of attention because of the negative pressure gradient, with high IAP against low CVP. According to the current literature, the danger of gas embolism is minimal. One newly published meta-analysis of short- and long-term outcomes after laparoscopic and open hepatic resections reported one gas embolism in 717 laparoscopic liver resections (LLRs) (0.1%)[49]. Other publications have reported gas embolism during LLRs; 2 earlier patients in a systematic review of a total of 182 published patients from 1991–2001[182], 1 patient out of 40 patients published by Tang in 2006[183], 1 patient out of 70 patients published by Dagher in 2007[6], and 2 out of 166 published by Bryant in 2009[184]. This gives a 0.1%–2.5% rate of clinically noticeable embolism although none of these led toany significant clinical problems. One report from China described a death during laparoscopic liver surgery that was believed to be a result of a CO_2 gas embolism[185], although no confirmation is available to rule out the possibility of another cause.

With an open venous vessel and an inviting pressure gradient, gas embolism is a possibility. However, some indications exist that embolism is not entirely the result of a pressure gradient[186]. First, the gas enters the right heart via the vena cava. From there, the gas will be brought with the bloodstream into the pulmonary circulation, and to some extent the gas will dissolve and increase the end-tidal CO_2. An occluding embolism in the pulmonary circulation influences the gas exchange, mainly by an increase in alveolar dead space. This happens because of continued ventilation of areas that do not have perfusion and affects CO_2 elimination by the lungs[187]. The change would be less if the tidal volume were not kept fixed, as done in the studies presented here. The ratio of dead space to the tidal volume offers the measurement of elimination of CO_2. This ratio (V_d/V_t) was increased during CO_2 embolism in an earlier study by our group, on the same porcine model as presented in this thesis[188]. There is a danger of interference with the gas exchange, cardiac arrhythmias, pulmonary hypertension, right ventricular strain, and eventually cardiac failure[189](Figure 12). Pulmonary vascular resistance (PVR) increases also with pulmonary embolism. Pulmonary arterial pressure (PAP) rises proportionally with the increase in flow in the remaining open part of the pulmonary circulation. A change in PAP is likely when the occlusion is 25–30% of the pulmonary vascular tree, and even below 25%, there are some minor changes[190]. Vasoactive amines (e.g., serotonin) may play a role in this increase in MPAP. Another possibility is the effect from baroreceptors situated in the pulmonary arteries, resulting in vasoconstriction[187].

A large volume of gas can block (form a "gas lock") the microcirculation in the lungs and thus give clinical signs, at least until the gas has resolved. The gas bubbles dissolve into the surrounding solvent. This process depends on several factors: (a) gas–liquid diffusion, (b) the universal gas constant, (c) saturation concentration of the gas, (d) the temperature, (e) surface tension, (f) ambient pressure, and (h) radius of the bubble[191]. The physics and physiology related to gas bubbles in the blood are extremely complex[192-194]. In bigger vessels, the gas bubbles are spherical, but by dislodging into smaller vascular structures, they become elongated. Several small bubbles can coalesce into a bigger or longer bubble, and the cylinder shape increases the dissolving time of the bubble. When the bubble diminishes by dissolving into the surrounding solvent, it is dislodged again into even smaller vasculature. This so-called "stick-and-slip" movement can be affected by the size of the bubble and possibly by some complex adhesive interactions by proteins sticking to the bubble surface[192].

The venous embolism can pass to the arterial circulation in two ways. In the case of massive embolism, the diffusion capacity decreases, and there can be overflow to the systemic circulation[195-197]; in the case of patent foramen ovale, which is found in up to 30% of people, the venous gas embolism will increase the pulmonary pressure so that the pressure on the right side of the heart will rise above the pressure on the left side, and the blood, with potential gas emboli, will flow from right to left[189]. Although pigs have almost the same prevalence of patent foramen ovale as humans[198], there was no focus on possible paradoxical embolism in the studies presented here.

When a gas embolism is in the arterial circulation, the embolus can cause pathologic changes in several ways: ischemic changes because of a blocked artery, mechanical stripping of endothelial cells with increased permeability, inflammatory response to the gas bubble by activation of complement and hence white blood cells, and activation of the clotting system[189, 191].

The use of an argon-enhanced coagulation (AEC) in open liver surgery has been accepted as an excellent method to reduce bleeding. But with adapting the same method to laparoscopic surgery and using the instrument in a closed pressurized space, problems arose. Because Ar is less soluble in blood than CO_2 (see Table 1), there was no surprise at reports of even more serious effects of this type of gas embolism. Near-fatal and fatal outcomes from Ar gas embolism during laparoscopic liver surgery have been described in case reports[199-203].

The treatment of a suspected gas embolism consists of cessation of gas insufflation, release of pneumoperitoneum, moving the patient into the left lateral position, and attempted aspiration of gas with a CVP catheter[175]. Emergency thoracotomy with internal cardiac massage and possible use of cardio-pulmonary bypass have been described[174].

Objectives

The particular aims of this study were as follows:

- To evaluate the efficacy and safety of established techniques for division of liver parenchyma, with a laparoscopic approach (studies I and IV).

- To study the differences of low versus high intra-abdominal pressure on bleeding and formation of venous gas embolism during laparoscopic liver resection (study II).

- To compare the effect of argon gas versus carbon dioxide on gas exchange and pulmonary circulation during an experimental liver resection (study III).

Animal model

Choice of animal

The pig is a good model for studying hepatic resections because of the similarities to humans. There are anatomical, physiological, and cardiovascular similarities; however, some skepticism is found regarding similarities in physiological response to pneumoperitoneum[204, 205], which can be, depending on different physiology in the prone position, intra-peritoneal differences and tolerance for pressure[205] or possible differences in elimination of CO_2, dependent on age and size[135]. Animal studies can give a direction for future human studies, and results should be extrapolated to humans with caution. For this reason, animal studies are ranked low in the pyramid of clinical evidence. Animal studies are a tool that can be divided into two groups: first, the experiments testing an effect of treatment and second, testing the mechanism of a treatment[206].

The liver in the pig is reasonably sized and has a similar anatomy to humans. A choice of a different animal, such as a rodent model, would not yield a reliable testing model for the same instruments used on humans and could therefore make comparisons more difficult.

National rules of ethics regarding animal research were followed in detail. All uses of animals in the presented studies were approved by the Local Ethics Committee on Animal Experiments in Uppsala, Sweden.

A specific attempt was made to reduce the number of animals used, in accordance with the "three R's" of ethical rules, by means of randomizing a few suitable animals into more than one study. For study II, there were four "historical" animals randomized into the 16-mmHg group, and in study III, 7 of the 8 animals in the CO_2 group were "historical" animals, randomized from a collection of suitable animals. A blinded note system was used to randomize animals from the group. The possible bias introduced by doing so was evaluated.

There were few problems with the quality of animals. Animal weights did not differ between experimental and control groups in any of the studies.

Anesthesia

The same method of anesthesia was used in all experiments. No obvious drift of the model was noticed between experiments although the danger of this is appreciated because a number of months passed between some of the experiments. The animals were fasted overnight with free access to water. Anesthesia was started with sedation, 50 mg xylazine 20 mg/mL (an $Alpha_2$-agonist, Rompun® vet., Bayer, Leverkusen, Germany) i.m. $Alpha_2$-agonist produces a sleep-like condition in combination with muscle relaxation and some degree of analgesic effects. A peripheral ear vein was cannulated for further induction and maintenance of anesthesia and for fluid administration. For induction of general anesthesia, piglets were given i.v. tiletamine/zolazepam (a blend of N-methyl d-aspartate receptor-antagonist and benzodiazepine both 50 mg/mL, Zoletil forte vet.® Virbac, Carros, France 6 mg/kg). This blend gives certain and effective anesthesia with few site effects. In addition, the animals received more xylazine 20 mg/mL (an $Alpha_2$-agonist, Rompun® vet. Bayer, Leverkusen, Germany) 2.2 mg/kg, and atropine sulfate 0.5 mg/mL (atropine is given before surgery to reduce salivation and bronchial secretions, to minimize bradycardia during intubation, or for the treatment of pylorospasms and spastic conditions; Atropin®, Mylan AB, Stockholm, Sweden), 0.04 mg/kg. Morphine hydrochloride 10 mg/mL (an opioid analgesic, Morfin Meda, Solna, Sweden) 20 mg and ketamine hydrochloride 50 mg/mL (a drug that gives dissociative anesthesia and strong analgesic effect, Ketalar®, Pfizer, Sollentuna, Sweden) 100 mg were given as an i.v. bolus. For maintenance of anesthesia, ketamine hydrochloride 50 mg/mL (Ketalar®, Pfizer, Sollentuna, Sweden) 20 mg/kg/h, pancuronium bromide 2 mg/mL (a muscle relaxant, Pavulon®, MSD, Sollentuna, Sweden) 0.24 mg/kg/h (in study I and II) and 0.12 mg/kg/h (in study III and IV), and morphine hydrochloride 10 mg/mL (Morfin Meda, Solna, Sweden) 0.5 mg/kg/h were administered as a continuous i.v. infusion. Ringer acetate was administered i.v. until the CVP reached 5 mmHg. All animals were intubated with a 7-mm tracheal tube with cuff (Hi-Contour™, Mallinckrodt Medical, Athlone, Ireland) and mechanically ventilated (Ventilator Servo 300 or 900C, Siemens Elema, Solna, Sweden) with an FiO_2 at 0.3 (30%). End-tidal CO_2 was measured (CO_2SMO plus, Novametrix Medical Systems Inc., Wallingford, CT, USA). Minute ventilation was adjusted to obtain a baseline $PaCO_2$ of 5.0–5.5 kPa, and 5 cm H_2O positive end expiratory pressure was used. The effectiveness of the anesthetics was checked with a pinch to the animal's foot.

The operation

For establishing the pneumoperitoneum, a Veress needle was always used. When steady state with pneumoperitoneum was reached, two 5-mm trochars, one on each lateral side of the abdomen, and two 10-mm trochars in the nipple line on both sides were inserted. A gas tube was attached to one of these to maintain pneumoperitoneum at a determined level. An Olympus® UHI (Olympus Optical Co., LTD, Tokyo, Japan) insufflator was used and was relayed on for holding the level as chosen. Its ability to hold the pressure was checked with a pressure meter to another trochar for several operations. Full agreement was observed between the pressure displayed on the insufflator and the measured pressure. A low pressure was defined as 8 mmHg and high pressure at 16 mmHg. An 8 mmHg value is lower than most hepatic surgeons choose for LLR, and 16 mmHg is higher but not as high as the highest IAP described during LLR[10].

For all the presented studies, the same laparoscopic resection was performed. The devices used, were adjusted to the settings recommended by the manufacturer. This resection started at the base of the left lobe and continued to the posterior borders of the lobe. A lobe of an average 143±43.6 g was removed. Study II and study III differed from studies I and IV in the way that intentional injury was made to the left liver vein with the objective of simulating an injury that could arise and could take some time to discover or manage. The vein was held open for 3 min before it was closed with metal clips on both sides and the resection finished. Three minutes seemed a reasonable time to simulate a clinical setting in which a vein is transected and some time is spent to react to possible bleeding and/or find the divided vein, especially during high IAP. The resected liver was left in the abdomen until after the experiment was finished, and the animal was killed. A laparotomy was then performed to retrieve the resected liver for weighing and to apply suction to measure blood/fluid in the abdomen.

Evaluation of embolism

How does one diagnose embolism in the best way possible? A method like precordial or esophageal auscultation, listening for the typical "mill-wheel" murmur, is not very reliable for diagnosing gas embolism with certainty. The auscultation is very subjective and probably does not detect a small-volume embolism. A change in end-tidal CO_2 suggests a change in the ventilation–perfusion relationship. Again, however, small embolisms are not detected with end-tidal CO_2 changes. In addition, there are very rapid changes in end-tidal CO_2 in case of an embolism, and these can be difficult to detect. PAP has also been suggested as an indicator for gas embolism but trans-esophageal ultrasound is a better alternative[207]. Doppler ultrasonography can be used to detect gas embolism, and some authors suggest the most sensitive and definitive method is the use of trans-esophageal echocardiography (TEE)[186, 207-209].

Trans-esophageal echocardiography

The ultrasound used in the presented studies was a Sonos 1000 Ultrasound System, Omniplane Probe, Hewlett Packard, Aliso Viejo, CA, USA (Figure 13). The probe placement was somewhat challenging, especially in low-weight animals. The lung in these animals interrupted the acoustic window. The detection of embolism was tested and confirmed in all animals by injecting a few milliliters of saline with a small amount of air shaken into the fluid. If a typical picture was not achieved (Figure 14), the best possible view was obtained with the help of a saline/air mixture injection. The amount of air in this mixture was negligible and not considered to have any effect on the experiments. A detection bias is recognized in the cases of difficult placement of the TEE where embolism could have been underestimated. The ultrasound probe had a 5.0-MHz transducer that could be rotated from 0 to 180°. Gas bubbles appear hyperechoic on the screen (Figure 14). The TEE detects everything that floats in the blood and has a different density from

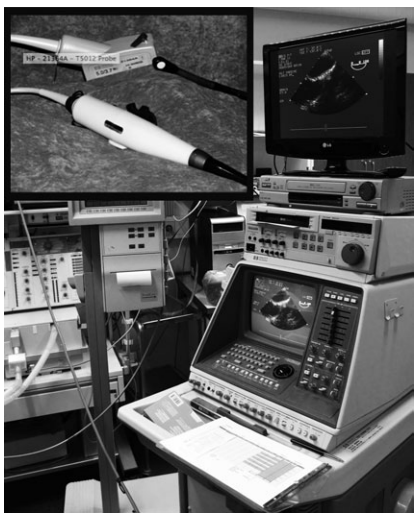

Figure 13. Sonos 1000 and Omniplane TEE probe from HP.

blood; thus, it does not differentiate among CO_2 and other gas embolism, fat embolism, or hyperechoic thrombotic emboli[166]. This lack of specificity has to be recognized to understand a possible detection bias. At the measurement of CO, the TEE detected the small bubbles in the cold saline. When CO measurements were made, a marker was placed into the TEE image as an aid to differentiate the hyperechoic bubbles following the fluid injection. These bubbles were usually smaller and less hyperechoic.

Two definitions had to be agreed on before experimental work was started: volume and length of embolism. The quantification of embolism seen on cross-sectional ultrasound is a challenge. An attempt to quantify was made as follows: grade 0 when <5 bubbles were seen in the lumen of the right atrium and/or pulmonary artery; grade 1 if there were ≥5 bubbles seen, without filling the lumen; and grade 2 if the lumen of the right atrium and/or pulmonary artery was filled. A similar, although less-decisive grading of embolism had been used before in the same model[210]. Different grading systems for embolism have been suggested by other authors[186]. This particular system was evaluated, with the conclusion that a simpler grading system would give less possibility for measurement bias. When embolism occurred, the timing started when >5 bubbles were seen. Changes during embolism, e.g., between grade 1 and grade 2, were noted and timed. When no bubble was seen in the lumen, the embolism had ended and no additional bubbles were seen for 10 s after that.

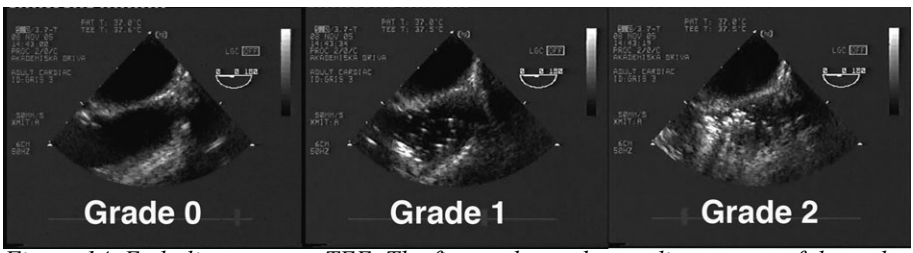

Figure 14. Embolism seen on TEE. The figure shows the grading system of the embolism.

This semi-quantitative method was the best available way to measure the amount of embolisms. Two persons viewed the videotapes for grading with variable time interval from the experiment. Although there was a possibility of these persons having knowledge about the operative method used, the fact was that most of the time the tapes were reviewed a long time after the experiment so the operative methods were not fresh in memory. A possibility of detection bias is recognized, although it is not assessed as a problem in this context. If disagreement arose, the two observers reviewed these episodes and agreed on the interpretation of what was seen.

Evaluation of bleeding

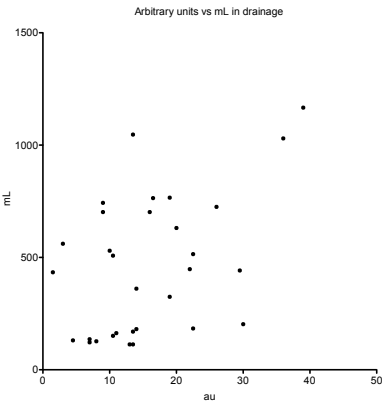

Figure 15. Correlation between measured amount of blood from CUSA™ and abdomen versus the observations of bleeding from the liver in arbitrary units. N=30 from studies II and IV; r=0.450, P=0.011.

Measuring the amount of suctioned blood from the surgical field and abdomen and adding the weight of fluid in used gauzes gives estimated bleeding in clinical settings. This estimation does not take into account other fluid loss into the abdomen during the operation. So this is not strictly estimation of bleeding but of total fluid loss in the abdomen, including the bleeding. The fact is that some of the piglets delivered for experimental use do have a considerable amount of fluid in the abdominal cavity. The goal in the presented studies was to evaluate only the bleeding from the liver without being influenced by the fluid in the abdomen. For the first two studies decision was made to evaluate the bleeding from the recorded videotapes as has been described earlier[210]. Two experienced surgeons, independent of each other, evaluated the videotapes in accordance with the established grading system. Blinding of method was not applicable, and possible detection bias is recognized. Every operation was divided into 1-min intervals and graded with the highest value seen in each minute. The value was given in arbitrary units. The observation key was as follows: no bleeding=0, oozing=1, and pulsating bleeding=2. In study I and II the values where used for calculation in a.u. Since the variables are strictly a categorical (ordinal), the allowed calculation is limitied. After publishing the results in a.u. a counting was undertaken of the different values and thereby the results were of numerical (discrete) type. Comparison could then be made between the groups, which gave the same results as published in the two studies. The fluid removed by the CUSA™ and from suction of the whole abdominal cavity was measured. The quality of the video assessment was tested with comparison of the methods. The Spearman correlation was calculated and showed a correlation between the amount of bleeding in milliliters and the semi-quantitative evaluation of videotapes in arbitrary units (a.u.) (r_s=0.450, P=0.011; see Figure 15). There was a good agreement calculated between the two observers. No coagulation tests were done on any of the animals. In study III and IV the amount measured from the abdominal cavity was used to evaluate bleeding with the possible bias that included.

Evaluation of gas exchange and pH

The evaluation of the gas exchange is of central interest regarding gas embolism. The only time there was a need for drawing blood for blood gas analysis was at the start of each experiment. This analysis gave the values of pH, PaO_2, and $PaCO_2$ in the animals' blood, and these were used to calibrate the online measurement system for these parameters, the Paratrend®. The Paratrend® sensor (Trendcare Monitoring System, TCM 17000®, Diametrix Medical Inc., Buckinghamshire, UK) was passed into the left carotid artery for continuous measurements of arterial pH, PaO_2, and $PaCO_2$.

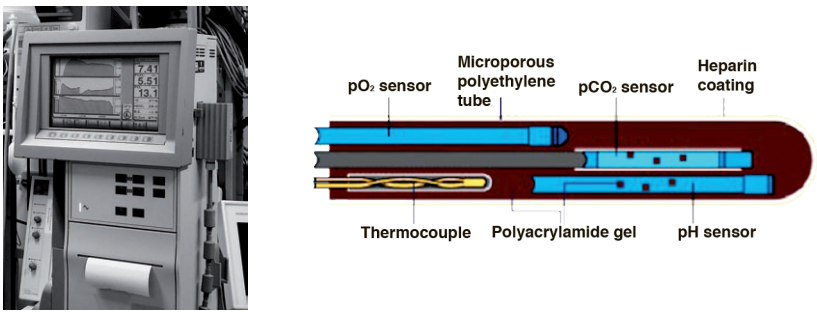

Figure 16. Left: Paratrend® with display and printer for results. Right: The construction of the Paratrend® probe.

The system consists of three optical fibers for measuring pH, PaO_2, and $PaCO_2$, and a thermocouple that measures temperature (Figure 16). The system has been evaluated by others, with excellent results compared to blood gas analysis[211].
The insertion of this heparin-coated, 0.5-mm microporous polyethylene line was done via an arterial cannula in the right external carotid artery (Figure 17). The line was placed 12 cm from the skin incision. The sensor line was fragile and the slightest bend to it could result in damage. With cautious insertion, this was usually not a problem. A change of sensor was time consuming because the line had to be calibrated by a specific method in accordance with the manual. The same sensor was reused several times.

Measurements of pulmonary and systemic hemodynamics

A pulmonary artery catheter (Swan-Ganz, CritiCath Ohmeda® Oxnard, CA, USA) and central venous line (BD Careflow™, Becton Dickinson Critical Care Systems, Singapore) were passed from the right jugular vein for measurements of CO, PCWP, PAP, and CVP. CO was measured with a thermal

dilution method where cold saline (around 8 °C) was injected[212]. An arterial catheter (Becton, Dickinson and Company, Franklin Lakes, NJ, USA; 18 G) was inserted into the right external carotid artery and then threaded into the aortic arch for pressure monitoring and blood sampling. Standard electrocardiogram, HR, temperature, arterial blood pressure (AP), and PAP were continuously monitored (Marquette, Solar 8000, Hellige Systems, Freiburg, Germany) and recorded (AcqKnowledge 3.8.1, StatSoft® Scandinavia AB, Uppsala, Sweden). (Figure 17).

Calculations

For calculations of MPAP, the equation MPAP=Diastolic PAP + 1/3(Systolic PAP–Diastolic PAP) was used.
PVR was calculated using PVR (dyn·s·cm^{-5})=80·(MPAP–PCWP)/CO.
For calculation of MAP, the equation MAP=Diastolic AP + 1/3(Systolic AP–Diastolic AP) was used.
SVR was calculated using SVR(dyn·s·cm^{-5})=80·(MAP-CVP)/CO).

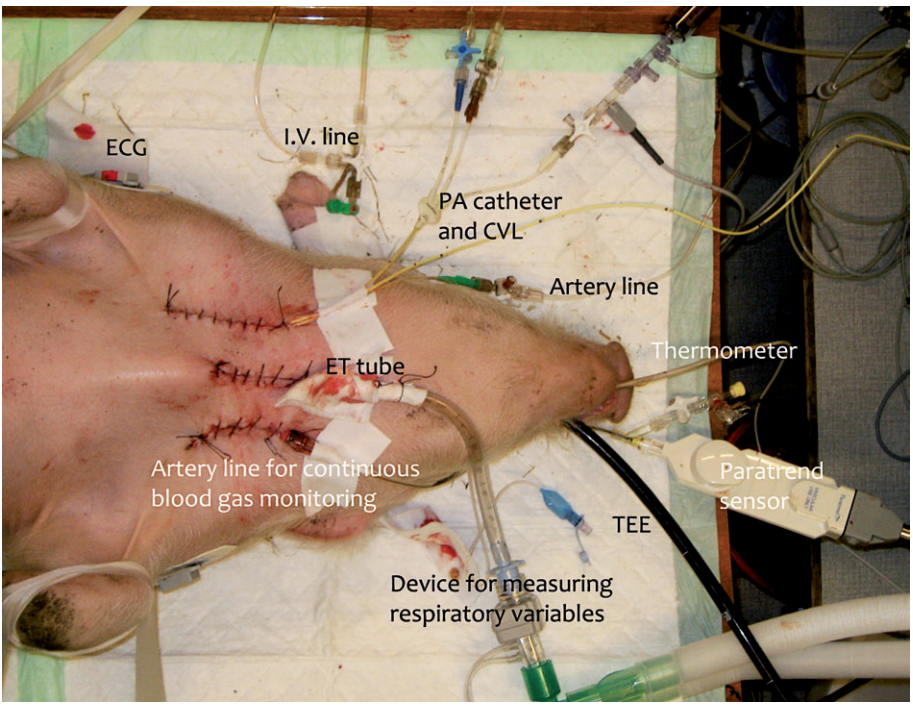

Figure 17. Overview of the animal model in all of the experiments.

Randomization and reduction of animal use

Randomization was made by means of a blinded note system. A sign was written on a piece of paper that was folded several times together and mixed with other notes in a non-opaque cup. One note was drawn for each animal. Where partly "historical" animals were used as controls (studies II and III), these animals were randomly chosen from a pool of earlier operated animals. This randomization was done by a numbered blinded note system in the same way. "Historical" animals filled in a group with other "new" animals. There was no detected difference between these animals.
Animals in study I were used for two publications, the operative point of view in study I and the anesthetic point of view in a study by Fors et al[188].

Statistics

The Gaussian distribution was tested with the D'Agostino & Pearson omnibus normality test (Prism® 5 for Macintosh OS X; GraphPad Software Inc., California, USA). For calculation of significance between two groups, a Mann–Whitney test was used for non-Gaussian distribution and a t-test for Gaussian distribution. For changes within the groups, a Wilcoxon matched-pair signed-rank test was used for non-Gaussian distribution and paired t-test for Gaussian distribution. For differences between more than two groups of measurements, the Kruskal-Wallis test was used. A Spearman correlation test was used for non-Gaussian distribution and Pearson's correlation for normal distribution for correlation tests. The Spearman partial correlation was used for correlation calculation where controlling of the third variable was needed.
A weighted Cohen's kappa coefficient was calculated for evaluating the agreement of observers judging the bleeding in the operations. Kappa is presented with 95% confidence intervals (CIs).
Statistical programs used for these studies were StatView for Windows version 5.0 (SAS Institute Inc.), Statistica® software (StatSoft, Tulsa, Oklahoma, USA), Prism® 5 for Mac OS X (GraphPad Software Inc., California, USA), and Instat® 3 for Macintosh (GraphPad Software Inc., California, USA).

Experimental protocol

Study I

Sixteen piglets were randomized into two groups. Both groups underwent laparoscopic left lobe resection, with IAP of 16 mmHg by CO_2 gas. One group was operated on with a combination of ultrasonic dissector (CUSA™) and ultrasonic scissors (Autosonix™) (group-US; n=7; one animal died of bleeding) and the other group with the combination of CUSA™ and the vessel sealing system (Ligasure™) (group-VS; n=8).

Equipment and lines for measurement of vital signs, systemic and pulmonary hemodynamics, and gas exchange were in place as explained earlier (see pages 42-43).

After completed preparations, animals were observed, usually for 30–45 min with no interventions to allow hemodynamic and respiratory stability. Baseline values were then obtained (steady state pre-operatively, SSPO), and thereafter CO_2 pneumoperitoneum was established. IAP was maintained at 16 mmHg. This was followed by a new stabilization period, and by the end of that a second set of baseline values (steady state at pneumoperitoneum, SSPP) was collected before the start of the operation. Recordings were made every 5 min during the operation, except for PCWP and CO, which were recorded every 15 min. The pulmonary and systemic APs, end-tidal CO_2, and temperature were monitored. Immediately after the operation, a set of recordings was made before the release of pneumoperitoneum. Data were recorded every 10 min for 30 min after release of pneumoperitoneum (see registration form, Appendix B). As mentioned earlier, a more detailed analysis of gas embolism and the effect of gas exchange and systemic and pulmonary circulation from this study is published elsewhere[188].

Operation time was registered. The operation was taped, and after the experiment, two independent, experienced surgeons evaluated the bleeding from the videotapes. One videotape in group-VS was missing. TEE recordings were also reviewed by two independent observers after the experiment.The semi-quantitative amount of embolisms was registered. Endpoints were the amount of bleeding and amount of embolisms.

Study II

Sixteen piglets were randomized into two groups receiving different IAPs. In group-H, there were four animals randomized out of a pool of "historical" animals. The same surgeon, following the same protocol for the same model, had operated these animals. Both groups received laparoscopic left lobe resection, with intentional injury to the left liver vein. (see page 38).

One group (group-L; n=8) was operated with an IAP of 8 mmHg pressure of CO_2 and the other group (group-H; n=8) with 16 mmHg pressure of CO_2. The favorable instruments from study I were used for parenchymal division, i.e., the combination of CUSA™ and Ligasure™.

Measurements of gas exchange and systemic and pulmonary circulation were performed as described earlier (see pages 42-43).

When the animal had been anesthetized, a period of approximately 30 min (variable between individual animals) was used to achieve hemodynamic and respiratory stability. When this was reached, a baseline measurement of PaO_2, $PaCO_2$, pH, end-tidal CO_2, CO, PCWP, HR, and CVP was registered. The pneumoperitoneum was then established and maintained at the IAP chosen for each group. PaO_2, $PaCO_2$, pH, end-tidal CO_2, HR, and CVP were registered every fifth minute of the operation, and CO and PCWP were measured and registered every fifteenth minute of the operation. When the operation was finished, the pneumoperitoneum was released. At that point, a measurement and registration of all parameters were undertaken and every tenth minute after that for 30 min (see registration form, Appendix B).

The operation was divided into specific time points, i.e., SSPO, SSPP, before venous cut (the last minute before injury; BVC), after venous cut (the first minute after closure of the injury; AVC), right after release of pneumoperitoneum (PPP), the tenth minute after PPP (PPP10), twentieth minute after PPP (PPP20), and 30 min after release of pneumoperitoneum (PPP30).

Calculations of MAP were done by first calculating the average systolic AP and average diastolic AP over a period of 1 min at the defined time points during the experiment. The same method was used for the calculations of MPAP then for the average of systolic and diastolic PAP. The calculations of PVR were also done in the same way, and the nearest measured CO and PCWP were used in the equation $PVR=80\cdot(MPAP-PCWP)/CO$.

Operating time was registered. Operations and TEE recordings were analyzed by two independent observers after the experiment.

The amount of embolisms was calculated as a percent of total operation time. The primary endpoints were amount of bleeding and embolism, and secondary endpoints were changes in gas exchange and systemic and pulmonary circulation.

Study III

Sixteen animals were randomized into two groups, group-CO_2 (n=8) and group-Argon (n=8). In an attempt to reduce the use of animals, seven piglets were randomized from the "historical" pool, and one was new in the CO_2 group. The same surgeon, following the same protocol for the same model, had operated these animals. Animals in both groups were operated on with a left lateral lobectomy, and an intentional injury to the left liver vein was made. (see page 38).
Measurements of gas exchange and systemic and pulmonary circulation were as described earlier (see page 42-43).
When the animals had been anesthetized, a period of approximately 30 min or as long as needed was used for each animal to reach hemodynamic and respiratory stability. When this was achieved, a baseline measurement of PaO_2, $PaCO_2$, pH, end-tidal CO_2, CO, PCWP, HR, and CVP was registered. The pneumoperitoneum was then established and maintained at 16 mmHg. Another set of the same parameters was measured when the animal had reached steady state after established pneumoperitoneum. Then PaO_2, $PaCO_2$, pH, end-tidal CO_2, HR, and CVP were registered every fifth minute of the operation. CO and PCWP was measured and registered every fifteenth minute of the operation (see registration form, Appendix B). A technical problem arose in one animal in group-Ar with the Swan-Ganz catheter, and PAP was not available after the vein injury in that particular animal so that calculating PVR and MPAP was not possible.
The operation was divided into periods as done in study II, i.e., SSPP, BVC, AVC, PPP, PPP10, PPP20, and PPP30. The difference from study III was that the average value of systolic AP, diastolic AP, systolic PAP, and diastolic PAP was calculated for the whole period, i.e., the average of these parameters at BVC was calculated from the appropriated values from the start of the operation until the venous injury and at AVC from the appropriate values from the closure of the vein and until the operation was finished. For PVR calculations, the closest value in time of CO and PCWP was used. The focus in this study was on the period from the SSPP until the end of the experiment.
Operation time was registered. TEE recordings were analyzed. There was not a focus on bleeding as an endpoint in this study because similar bleeding was expected in both groups. To ensure that this was the case, the volume suctioned with CUSA™ and from the abdominal cavity at the end of the experiment was measured and compared in both groups.
The amount of the gas embolisms was calculated as a percent of operation time. Endpoints were effects on gas exchange and systemic and pulmonary hemodynamics.

Study IV

Sixteen animals were randomized into two groups. One group was operated on with the application of vascular staple device (Endo-GIA™, Universal 12 mm, Autosuture, CT, USA) to divide the liver parenchyma (Group-S; n=8), and the other was operated on with a standard combination of CUSA™ and Ligasure™ (Group-L; n=8) as used in previous studies. For the staple technique, three 60-mm and one 45-mm vascular stapler were used.

Animals in both groups underwent a left lateral lobe resection in the same manner as described in study I, without any intentional injury to the left liver vein. Measurements of gas exchange and systemic and pulmonary circulation were as described earlier (see pages 42-43).

When the animals had been anesthetized, a period of approximately 30 min or as long as needed was used for each animal to reach hemodynamic and respiratory stability. When this was achieved a baseline measurement of PaO_2, $PaCO_2$, pH, end-tidal CO_2, CO, PCWP, HR, and CVP was registered. The pneumoperitoneum was then established and maintained at 16 mmHg. Measurement of mentioned variables was repeated at steady state after established pneumoperitoneum. PaO_2, $PaCO_2$, pH, end-tidal CO_2, HR, and CVP were registered every fifth minute of the operation, and CO and PCWP were measured and registered every fifteenth minute of the operation (see registration form, Appendix B).

The experiment was divided into the following periods: SSPO, SSPP, 5-min intervals during the resection, PPP, and every tenth minute after that (PPP10 and PPP20) or until 30 min later (PPP30). The means of diastolic and systolic AP and PAP of each 5-min period during the operation were used to calculate MAP and MPAP, respectively. The same was done for the calculations of PVR, and the closest value in time of CO and PCWP was used for calculation.

Operating time was registered. TEE recordings were analyzed. The duration of embolism was calculated as the percent of operation time. Bleeding was measured from the the volume suctioned with CUSA™ and from the abdominal cavity at the end of the experiment and compared in both groups

The primary endpoint was amount of bleeding and gas embolism.

The secondary endpoint was change in gas exchange and systemic and pulmonary hemodynamics.

Results

Study I

There was no difference between the groups in basic parameters (Table 2). There was good agreement of bleeding evaluation between observers; the kappa calculated for the agreement of observers was 0.68 (CI: 0.53–0.82). The bleeding was increased during resections, with the combination of CUSA™ and Autosonix™ (group-US) and a trend toward longer operating time compared to the combination of CUSA™ and Ligasure™ (group-VS).

Table 2. Results of animal weight, specimen weight, operation time, and intra-operative bleeding in study I.

	Group-US	**Group-VS**	**P**
Animal weights in kg (range)	27.8 (25.4–30.2)	27.6 (24.3–29.9)	0.82
Specimen weight in g (range)	170 (127–328)	144 (115–252)	0.20
Operation time in min (range)	43 (24–64)	36 (24–44)	0.08
Intra-operative bleeding in arbitrary units (range)	35 (29–49)	21 (18–29)	0.02

Embolism was detected in 10 of 15 animals. Three animals in group-VS and two animals in group-US did not show any signs of embolism. By expressing the results in seconds, as done in the published article, there was a trend toward more grade 1 embolism in group-US (P=0.080). No difference was identified regarding grade 2 embolisms (P=0.380) although this analysis did not take into account the length of the operation. By measuring the length of the embolisms as a percent of the total operation time, there was no difference between the groups (P>0.200) for both grade 1 and grade 2 embolisms.

The same result was seen with counting the number of embolisms (Figure 18).

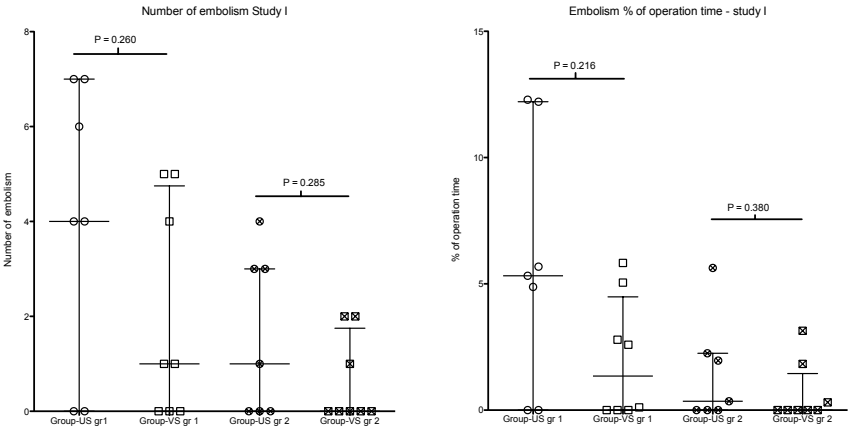

Figure 18. The number of embolisms (left) and the variation as a percent of operation time (right) for both groups. To the left in each graph is the grade 1 embolism and to the right the grade 2. Scatter graph, showing median value as a line and whiskers representing inter-quartile range.

Both combinations of instruments made liver resection feasible and generally safe. Both combinations gave satisfactory results. There was one death at the start of one operation, which could not be blamed on any of these instruments. An injury to the portal vein occurred because of a lack of care in manipulation of the liver.

Study II

Sixteen animals underwent laparoscopic left liver resection. No deaths occurred. There were no baseline differences between the groups (Table 3).

Table 3. Animal weight and specimen weight in study II.

	Group-L	**Group-H**	**P**
Animal weight in kg (range)	25.5 (24.2–29.4)	27.2 (22.5–32.7)	0.600
Specimen weight in g (range)	139.8 (90–188)	137.5 (94–173)	0.916

There was good agreement between observers in evaluation of bleeding: kappa=0.72 (CI: 0.59–0.84).

Bleeding

More bleeding was detected in the low pressure group at 0.82 a.u./min (0.32–0.96) vs. 0.38 a.u./min (0.09–0.84) (P=0.016) during the transection. Analysis of the bleeding in the defined parts of the operation identified more bleeding during the vein injury than other parts of the operation in both groups. Groups differed significantly regarding bleeding in the part before the vein injury (Figure 19). There was noticeably less bleeding in the animals that had embolism during the vein cut. Calculating the correlation between the bleeding and embolisms for each part resulted in a negative value for Spearman's r although it was not significant.

There was typically a pulsating bleeding from the injured vein in group-L and little or no bleeding in group-H, more like the blood was moving back and forth in the opening (Figure 20 and videos at: http://gasembolism.blogspot.com/).

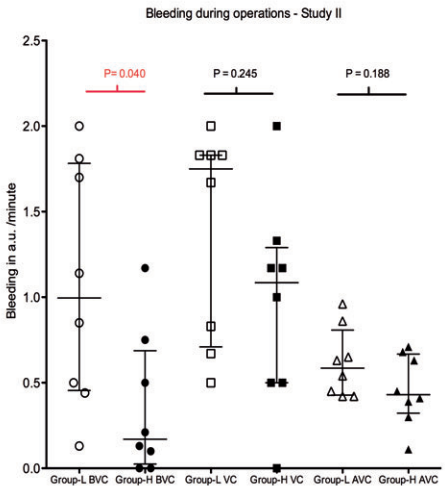

Figure 19. Showing bleeding in low pressure group (clear dots) and the high pressure group (filled dots), at various stages of the operation. The line represents the median value and interquartile range.

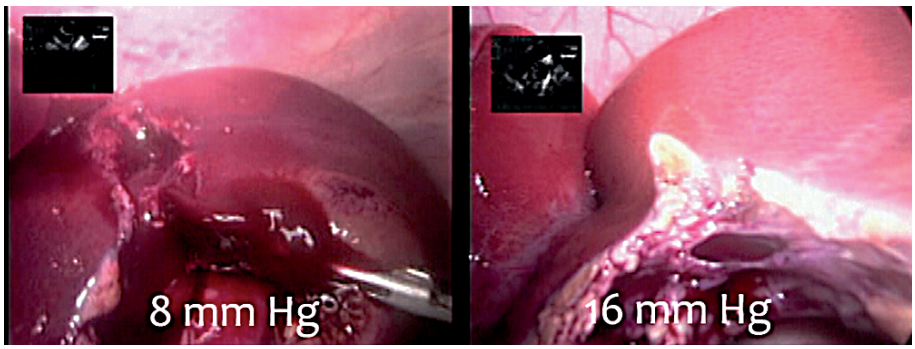

Figure 20. Bleeding seen on the video on the left from an animal in the 8-mmHg group (group-L) and on the right side from an animal in 16 mmHg group (group-H).

Embolism

There were increased, more frequent, and longer lasting embolisms in the high pressure group, both grade 1 and grade 2. Two animals in the low pressure group showed some sign of embolism. One of those showed signs only for 4 s (0.2% of operation time), and the embolism in the other animal lasted for 66 s (3.9% of operation time). No animal had grade 2 embolism in Group-L. All animals in group-H showed some degree of grade 1 embolisms, and five animals had grade 2 embolisms (Table 4)

Table 4. Embolism during operations in study II. Values are represented as median (range).

	Group-L	**Group-H**	**P**
Number of grade 1 embolism	0 (0–8)	17.5 (5–58)	0.001
Number of grade 2 embolism	0	1(0–6)	0.012
Embolism grade 1 as % of total operating time	0.0 (0.0–3.9)	14.1(2.6–53.8)	0.001
Embolism grade 2 as % of total operation time	0.0	2.3 (0.0–19.1)	0.012

Embolism was most frequent in the last part of the liver resection (AVC) where the liver tissue was thicker (Figure 21).

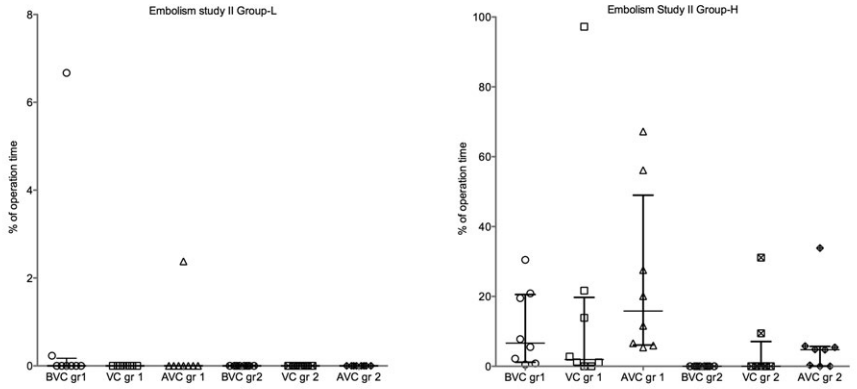

Figure 21. Embolisms during specified periods of LLR. Graph on the left: group-L, where there was minor embolism. Graph on the right: group-H with the most embolisms happening in the last part of the operation. The y-axis shows the percent of the operation time in each specified period. Lines represent the median value and interquartile range. No animal showed grade 2 embolism before the vein injury. Using the Kruskal–Wallis test, there was no significant difference within group-H regarding grade 1 embolisms, but there was significant variation within the same group regarding grade 2 embolism (P=0.016), showing that the different number of embolisms is more than would be expected from a random sampling. A significant difference was found between the BVC and AVC (P<0.05).

Gas exchange

pH

Both groups showed a fall in pH by a median 0.035 in group-L and 0.055 in group-H (P<0.025) after establishment of the CO_2 pneumoperitoneum. There was more effect on the pH in the high pressure group although no significant variation between the groups until after the vein injury. The largest difference was just after the release of pneumoperitoneum with a median pH of 7.41 in group-L and 7.33 in group-H. The pH increased from PPP in both groups

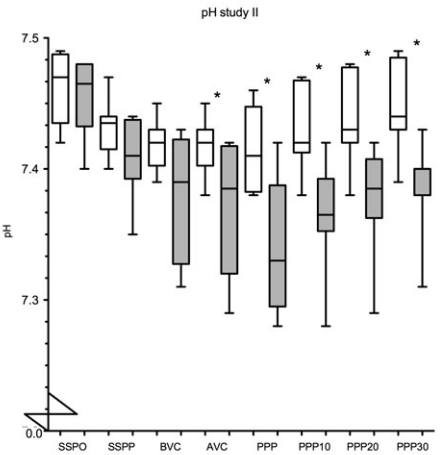

*Figure 22. Box plot of pH during study II. Clear boxes represent group-L and grey boxes represent group-H. The boxes show interquartile range and median value. The whiskers show 10–90th percentiles. Significant differences between the groups are marked with *.*

although a difference between the groups remained until the end of the experiment or 30 min after the release of the pneumoperitoneum (Figure 22).

$PaCO_2$

With introducing CO_2 into the peritoneum, the $PaCO_2$ rises, as was seen in both groups where the $PaCO_2$ in group-L increased from a median 5.27 to 5.83 KPa and from 5.31 to 6.08 KPa ($P<0.009$), between SSPO and SSPP, respectively. There was a further rise in $PaCO_2$ from the steady state of pneumoperitoneum and until the first part of the operation in both groups ($P<0.025$). In group-L, the highest median $PaCO_2$ value of 6.03 KPa was measured just before vein injury. In group-H, the highest median $PaCO_2$ value of 6.32 KPa was measured just after the release of pneumoperitoneum. From the first part of the operation, there was a difference between the groups, and this difference continued until the end of the experiment, 30 min after the release of pneumoperitoneum (Figure 23). The $PaCO_2$ had decreased to pre-operative values at the end of the experiment in group-L ($P=0.250$); however, in group-H, this was not the case, with median $PaCO_2$ measured at the end of the experiment at 6.34 KPa, 1.03 KPa above the pre-operative value (Figure 23).

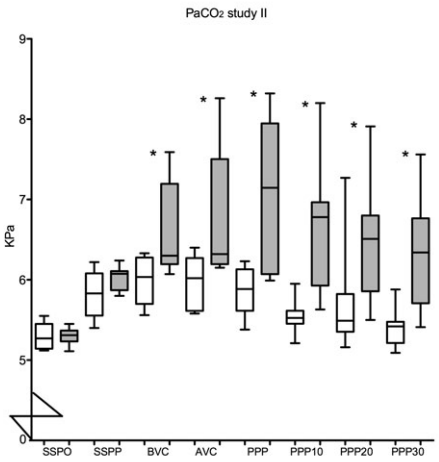

*Figure 23. Box plots of $PaCO_2$ in study II. Clear boxes represent group-L and grey boxes represent group-H. The boxes show interquartile range and median value. The whiskers show 10–90th percentiles. Significant differences between the groups are marked with *.*

PaO_2

The changes in the PaO_2 are the opposite of that for $PaCO_2$. With introducing CO_2 into the peritoneum, the PaO_2 fell in both groups. In group-L, a fall from 21.5 KPa to 19.9 KPa was observed, and in group-H, a fall from 20.7 KPa to 15.9 KPa was seen ($P<0.009$). A further fall was seen in $PaCO_2$ between the steady state of pneumoperitoneum and the first part of the operation ($P<0.025$).

Although there was a trend toward a difference between the groups after the vein injury ($P=0.070$), there was not a significant difference until after the release of the pneumoperitoneum. This difference remained until the end of the experiment. After the exsufflation, PaO_2 increased again. Neither group

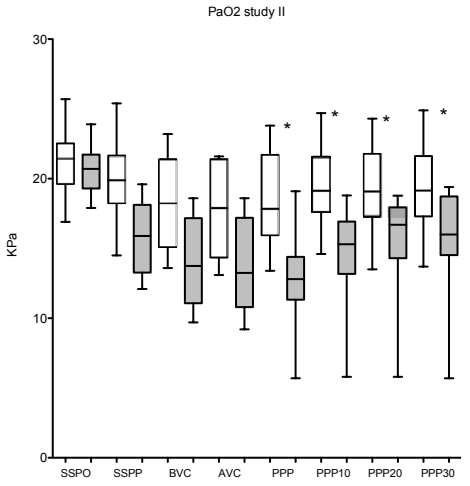

*Figure 24. Box plots of PaO_2 in study II. Clear boxes represent group-L and grey boxes represent group-H. The boxes show interquartile range and median value. The whiskers show 10–90th percentiles. Significant differences between the groups are marked with *.*

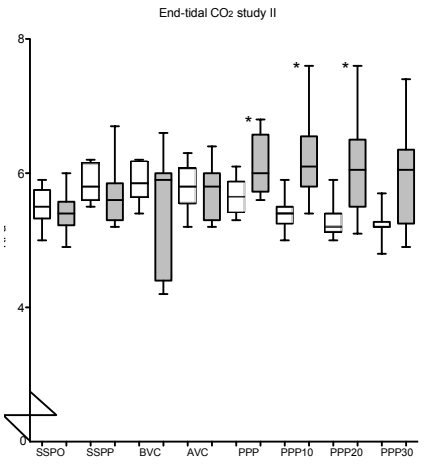

*Figure 25. Box plots of end-tidal CO_2 in study II. Clear boxes represent group-L and grey boxes represent group-H. The boxes show interquartile range and median value. The whiskers show 10–90th percentiles. Significant differences between the groups are marked with *.*

had reached the pre-operative value at the end of the experiment. The difference between the pre-operative value and the value at PPP30 was 2.0 KPa for group-L and 4.7 KPa for group-H, P=0.008 for both groups (Figure 24).

End-tidal CO_2

The end-tidal CO_2 increased somewhat in group-L (P=0.034), and there was a trend toward a rise in group-H (P=0.052). There was no difference between the groups concerning end-tidal CO_2 from pneumoperitoneal steady state to the start of the operation (P>0.300). However, at the end of the operation, when pneumoperitoneal pressure was released, there was a difference in the groups lasting 20 min after that. At PPP, group-L had an end-tidal CO_2 of 5.7 KPa and group-H had 6.0 KPa (P=0.025). Group-L fell under the basal value at the end of the experiment (P=0.021). In group-H, the end-tidal CO_2 rose between the last part of the operation and the release of the pneumoperitoneum (P=0.049). It stayed high until the end of the experiment, without further changes. There was a trend towards a difference between the groups at PPP30 (P=0.070) (Figure 25).

Hemodynamics

Systemic hemodynamics

Heart rate

There were no differences between the groups regarding HR during the operation. No significant changes were registered within the groups except for a gradual fall of 20 beats/min in group-L between the pre-operative value and the last measurement in the experiment (P=0.021) (Figure 26).

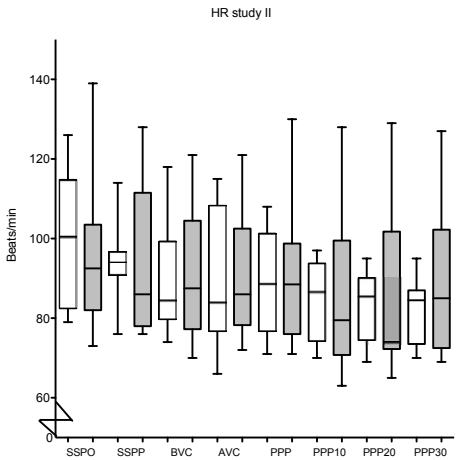

Figure 26. Box plots of HR in study II. Clear boxes represent group-L and grey boxes represent group-H. The boxes show interquartile range and median value. The whiskers show 10–90th percentiles. No significant differences were found between the groups.

Central venous pressure

The CVP rose by the increased abdominal pressure of CO_2. There was more increase in group-H with the higher IAP, from a median 7 mmHg to 9.5 mmHg in group-L compared to median 7 mmHg to 12 mmHg in group-H, P=0.021 and P=0.014, respectively. The CVP fell again before the vein injury and was then unchanged during the resection until the release of the pneumoperitoneum, when it fell in both groups. There was a difference between the groups from the start of pneumoperitoneum until 10 min after the gas was released from the abdominal cavity. The CVP in group-L had not returned to the basal value when the experiment ended (P=0.022) after having fallen below that value at PPP (P=0.014). However, the CVP in group-H, which had fallen below the basal value at PPP10 (P=0.020), did return to the pre-experimental value at the last measurement before the end of the experiment (P=0.105). (Figure 27).

By comparing the CVP to the IAP (8 mmHg or 16 mmHg) the IAP–CVP gradient could be estimated (not included in the published article). This estimation is particularly interesting in consideration of the hypothesis that embolisms happen with positive differences (positive gradient) between these two variables. For both groups, the IAP was constant although the changes with breathing increased IAP somewhat. This change did not exceed 1–3 mmHg. By looking at each animal and comparing the IAP (constant) and CVP (maximal, mean, and minimum) values, while also marking the

vein injury and the embolisms, one could see the relationship between these parameters. Figure 28(a) shows the only piglet in group-L that did have more than one embolism during the operation. When the embolism happened during the BVC, the IAP was below the mean CVP. The minimum CVP was at the same level as the IAP. Thus, there was no or a negative pressure gradient. After the vein injury, there was another embolism, and when that happened, the CVP (maximum, mean, and minimum) was below the IAP, at least in the beginning of this sequence of embolisms.

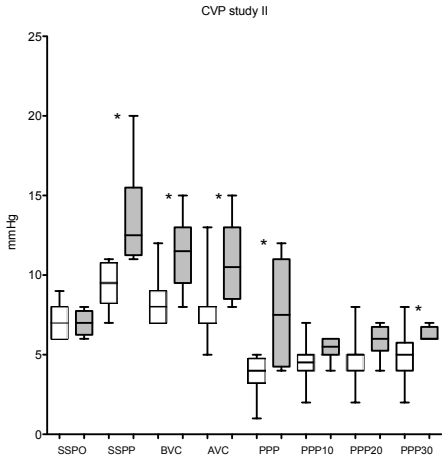

*Figure 27. Box plots of CVP in study II. Clear boxes represent group-L and grey boxes represent group-H. The boxes show interquartile range and median value. The whiskers show 10–90th percentiles. Significant differences are marked with *.*

The values of animals in group-H were compared in the same way. Figure 28(b) shows the animal that had the most grade 2 embolisms. The minimum and mean CVP values were below the IAP, but the maximum CVP was above IAP throughout the operation. By looking at one animal from group-H that had the lowest number of embolisms (Figure 28(c)), there still was an IAP–CVP_{min} and IAP–CVP_{mean} of more than 8 mmHg even when the animal did not show any embolisms.

Looking at one typical animal from group-L that did not show any embolism at all (Figure 28(d)), even here the CVP_{mean} and CVP_{min} are below the IAP with a gradient of >3 mmHg at the end of the operation.

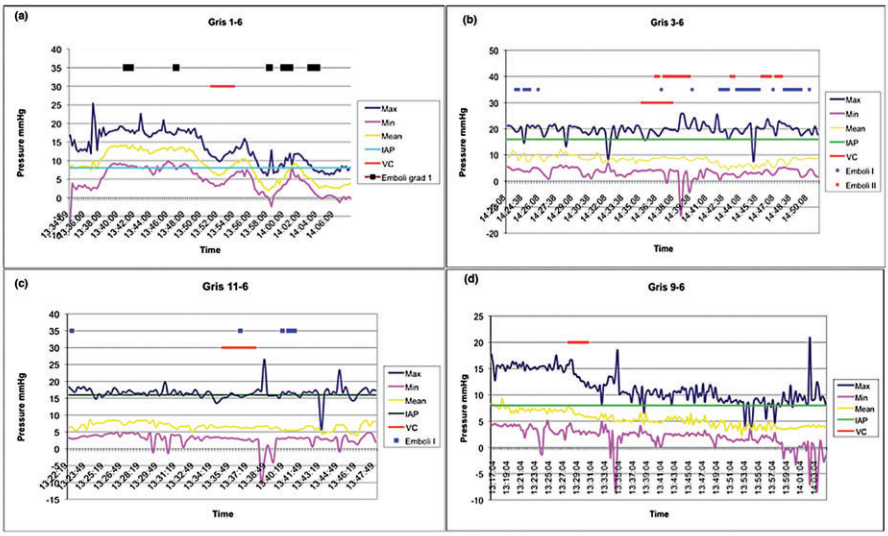

Figure 28.

(a)The interaction between IAP (8 mmHg) and CVP (maximum, mean, and minimum) during an operation on a piglet in group-L. This animal was the only animal that had more than one embolism during the experiment.

(b)Animal number 3–6 was the animal in group-H that showed the most grade 2 embolisms, shown in the figure as red dots. The maximum CVP was above the IAP (green line); however, the mean and minimum CVP were at least 4 mmHg below IAP.

(c) This animal was the one in group-H that had the lowest number of embolisms during the operation. The figure shows a quite stable line of CVP_{mean} and CVP_{min} at least 8 mmHg below the IAP both during embolism periods and when no embolisms were detected.

(d) A typical animal from group-L, showing no embolism but still with a positive IAP–CVP gradient.

Cardiac output

There was no change in CO in group-H during the whole experiment (Figure 29). In group-L, the CO fell between the measurement just after the vein injury and the measurement at the point of release of IAP (P=0.022). CO had not reached the basal value in group-L by the end of the experiment, 30 min after the operation (P=0.022). In one piglet, it was not possible to measure

CO from the AVC time point because of a technical failure. No difference was detected between the groups.

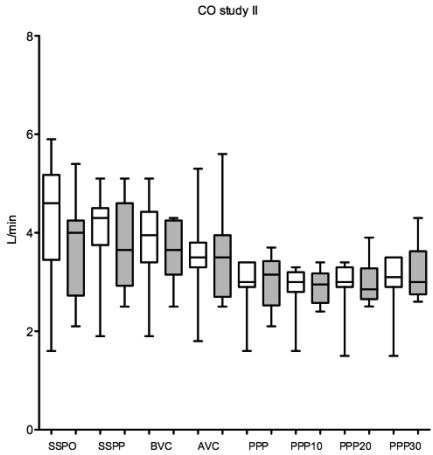

Figure 29. Box plots of CO in study II. The boxes show interquartile range and median value. The whiskers show 10–90th percentiles. No differences were found between the groups..

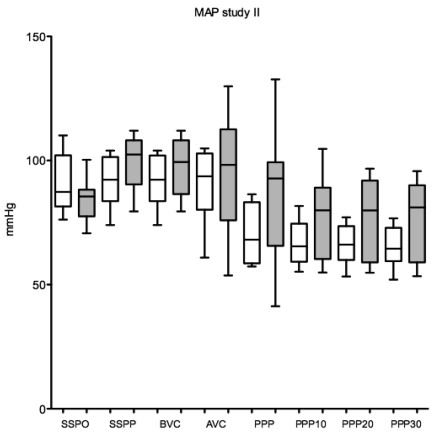

Figure 30. MAP during study II. No change was seen in group-H. In group-L, the MAP fell at the end of the operation and was not returned to the basal value at the end of the experiment.

Mean arterial pressure

There was no difference in MAP between the groups during the entire experiment. The MAP increased when pneumoperitoneum was introduced in group-H but was unchanged in group-L at the same time. However, there was a fall in MAP between the measurements at AVC and the release of the peritoneum in group-L; this was not the case in group-H where the blood pressure did not change by the freeing of the IAP. In group-L, the MAP was lower than the pre-operative value at the end of the experiment. There was no change in the MAP in group-H (Figure 30).

Pulmonary hemodynamics

Mean pulmonary arterial pressure

There was a rise in MPAP by 9.1 mmHg in group-H, from 13 mmHg at the pre-operative steady state and to 22.1 mmHg at the steady state after established pneumoperitoneum (P=0.008). A trend toward an increase was seen in

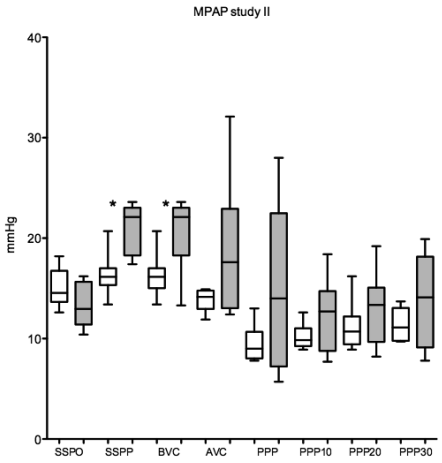

Figure 31. MPAP during study II. There was a significant rise in MPAP with the introduction of pneumoperitoneum in group-H. In group-L, there was a fall in MPAP during the resection. Significant differences between the groups are marked with.*

group-L, from 14.6 mmHg to 16.2 mmHg (P=0.055) at the same time. In group-H, there was a trend toward a decrease between AVC and PPP (P=0.055), and then the value was unchanged until the end of the experiment. The last measurement at PPP30 was not different from the basic value before the operation in group-H. When the operation was ongoing in group-L, the MPAP fell between the measure points before vein injury and after, from 16.2 mmHg to 14.2 mmHg (P=0.030), and it decreased even more between the AVC and PPP, from 14.2 to 9.0 mmHg (P=0.008). At PPP, it began to rise again but did not reach the baseline values at the end of the experiment (P=0.014) (Figure 31).

Pulmonary vascular resistance

PVR calculated as dyn·s·cm^{-5} did not change significantly from the basic value in group-H. There was a trend toward increase in PVR from steady state pre-operatively and to the steady state after pneumoperitoneum was established in that group (P=0.078). Further, in group-H, a trend was detected for a fall in PVR between the twentieth and thirtieth minutes after the release of the CO_2 from the abdominal cavity (P=0.078).

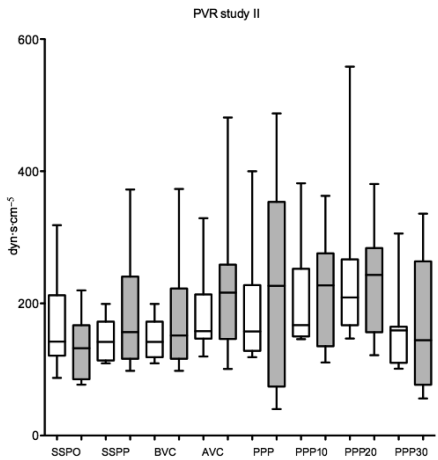

Figure 32. Box plot showing PVR. The whiskers represent 10th and 90th percentiles and boxes, interquartile range. No statistical difference was found between the groups.

In group-L, the PVR was unchanged during the whole operation; however, after the release of pneumoperitoneum, there was an increase between the measurements at the tenth and twentieth minutes (P=0.016) and a decrease between the

twentieth and thirtieth minutes (P=0.016). There was no difference between the groups at any of the measured points (Figure 32).

Study III

The animal weight in study III was the same in both groups. Group-Ar had a median weight of 27.9 kg (24.5–31.3 kg) and group-CO_2 27.2 kg (22.5–32.7 kg) (P=0.674). The same was the case for the weight of the resected liver (140.5 g, 121–226 g) and 134.0 g, 94–173 g), respectively (P=0.371).
There was not a significant difference between the groups regarding the operation time; median 31.5 min (range: 20–39) for group-Ar and median 25.5 min (range: 16–35) for group-CO_2 (P=0.115).
The operation time was similar in both groups; 30.5 minutes (20–39) in group-Ar vs. 24.6 minutes (16–35) in group-CO_2 (P=0.104).

Embolism

Although there were larger numbers of detected grade 1 embolisms in group-CO_2 than in group-Ar, median 16 (5–27) versus 3.5 (0–26) (P=0.035), respectively, the length of grade 1 embolisms as a percent of the total operation time was not different between the groups (P=0.879). Grade 2 embolisms did not differ in number or length. By looking at the embolisms during each stage of the operation, there was no difference between the groups. Six of eight (75%) animals in group-Ar showed grade 1 embolisms and 4/8 (50%) grade 2 in the same group. In group-CO_2, all animals (100%) showed grade 1 embolism and 5/8 (62.5%) grade 2.

Bleeding

Bleeding was similar in both groups; median 716 mL (390–1285 mL) for group-Ar and 595 mL (434–1047 mL) for group-CO_2 (P=0.500).

Systemic hemodynamics

Mean arterial pressure

There was no difference between the groups after establishing the pneumoperitoneum, although there was a trend toward higher MAP in group-CO_2 (P=0.052). There was a rise in MAP of a median 6.8 mmHg, from steady state after the start of the pneumoperitoneum until the first part of the operation, in group-CO_2 (P=0.039). At the same time, there was a trend for a rise of 8.9 mmHg in group-Ar (P=0.055). Between the first and the second parts of the operation, there was a median fall of 20.3 mmHg (21.5%) in group-Ar (P=0.008). At the same time, there was no significant change in group-CO_2, and this was the only point in the experiment at which there were significant differences between the two groups (P=0.015) (Figure 33).

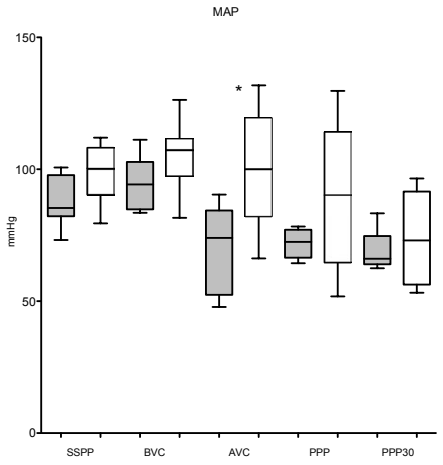

*Figure 33. Box plot of MAP during the experiment. Clear boxes represent animals in group-CO_2, and the grey group-Ar. Median value presented as a line and whiskers showing the 10^{th} and 90^{th} percentiles. Significant difference is represented with *.*

Heart rate

At no point during the experiment was there a difference in HR between the groups. Between the measure points, before and after vein injury, group-Ar showed a rise in HR of a median 12 beats per minute (from 73 to 85, 16.4%) (P=0.016), and the HR fell gradually from AVC to PPP and from PPP to PPP30 (P=0.047 and P=0.042, respectively) (Figure 34).

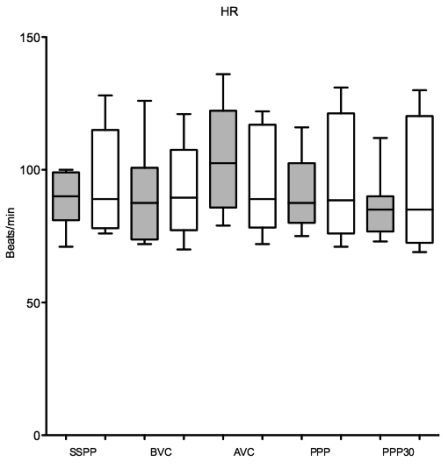

Figure 34. Box plots showing the HR during study III. Median values presented as lines and whiskers showing the 10^{th} and 90^{th} percentiles. No difference was found between the groups, although there were some significant changes within the group-Ar.

Central venous pressure

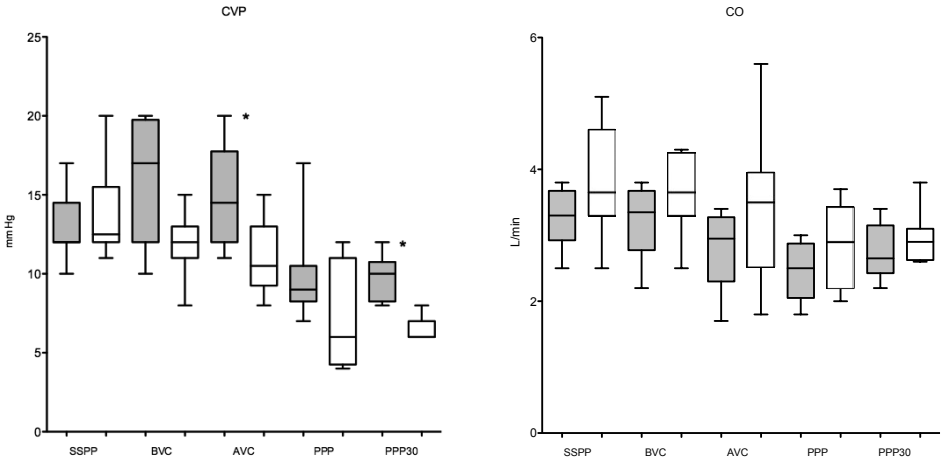

Figure 35 (left) Box plot showing CVP. Clear boxes represent group-CO_2 and grey boxes group-Ar. Median values presented as lines and whiskers showing the 10th and 90th percentiles. Significant differences between the groups marked with.*

Figure 36 (right) Box plot showing CO. Clear boxes represent group-CO_2 and grey boxes group-Ar. Median values presented as lines and whiskers showing the 10th and 90th percentiles. No differences were measured between the groups.

No significant change was seen in either of the groups from the steady state after established pneumoperitoneum, until the release of the pneumoperitoneum, when CVP fell in both groups (P=0.022) and remained at that level until the end of the experiment. There was a difference between CVP in the groups after the vein injury (P=0.031) and at the end of the 30-min observational period (P=0.001) (Figure 35).

Cardiac output

CO was without any difference between the groups. There was a fall in CO in group-Ar between BVC and AVC (P=0.028) and again between AVC and PPP (P=0.042). Between the two last measurements in the experiment, the CO increased in group-Ar (Figure 36).

SVR

No difference was found in SVR between the groups. At AVC there was a trend toward decrease in SVR (P=0.071).

Pulmonary hemodynamics

Mean pulmonary arterial pressure

The MPAP was not different between the groups at the steady state after established pneumoperitoneum, and no change was seen at the period before the vein injury; however, at the period after the vein injury, there was a significant difference between the groups. In the measurement at AVC, the animals in group-Ar had an increase in their median MPAP from 22.1 to 41.9 mmHg from the measurement at BVC, a rise of 19.8 mmHg (89.6%); however, this was not statisticly significant and must be accounted as a trend (P=0.055). Then there was a fall of 9 mmHg (18.6%) between AVC and PPP (P=0.011) and a further fall of a median 13.7 mmHg (41.6%) between the two last measure points in the experiment (P=0.031). The MPAP also fell in

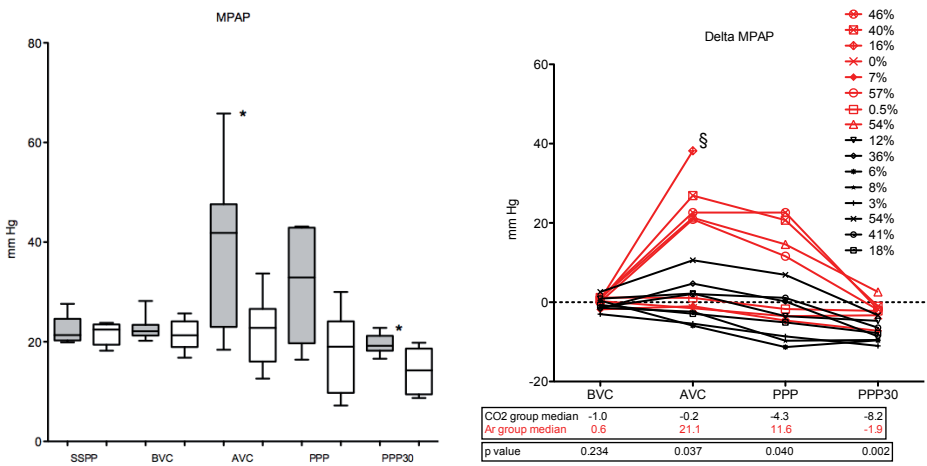

*Figure 37. On the left side is a box plot showing the MPAP. Clear boxes represent group-CO_2 and the grey boxes group-Ar. Median values presented as lines and whiskers showing the 10^{th} and 90^{th} percentiles. Significant differences between the groups are marked with *. On the right side is delta MPAP shown for each animal. Each red line represents on animal in group-Ar, and each black line represents an animal in group-CO_2. The one line ending at AVC marked § represents the animal in which technical difficulties arose regarding measuring the PAP. The number of embolisms is shown in % of total operation time for each animal. This includes both grade 1 and grade 2 embolisms.*

group-CO_2 between the AVC and PPP, a decrease by a median 3.8 mmHg (16.7%) (P=0.001) and a further decrease of median 4.8 mmHg (25%) between the last two measuring points (P=0.042) (Figure 37, left).

The change in the MPAP and comparison to the total number of embolisms in each animal is shown on the right side in Figure 37. There was a strong

correlation between the number of Ar embolisms and the rise in MPAP; Spearman's partial correlation, r=0.752, P=0.001 at AVC, and r=0.820, P<0.001 at PPP.

Pulmonary vascular resistance

No dissimilarity was detected in PVR between the groups in the first two stages of the experiment (P>0.080). Also, there was no change within the

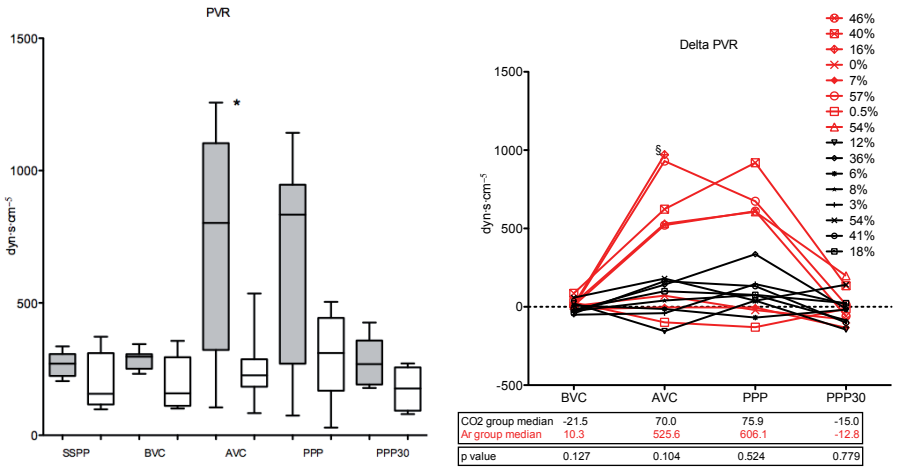

*Figure 38. On the left side: Box plot showing the PVR. Clear boxes represent group-CO_2 and the grey boxes group-Ar. Median values presented as lines and whiskers showing the 10th and 90th percentiles. Significant differences between the groups are marked with *. On the right side: delta PVR shown for each animal. Each red line represents on animal in group-Ar, and each black line represents an animal in group-CO_2. The one line ending at AVC marked § represents the animal in which technical difficulties arose regarding measuring the PAP. The total number of embolisms is shown in % of total operation time for each animal. This includes both grade 1 and grade 2 embolisms.*

groups between SSPP and BVC (P>0.078). Based on the measurement at AVC, group-Ar showed a considerable increase by median 505 dyn*s*cm^{-5} (169%) (P=0.039). At the same time, no alteration was seen in PVR in the group-CO_2 (P=0.250). The level of PVR in group-Ar was also increased at PPP without any significant change from AVC. At the thirtieth minute after the release of the pneumoperitoneum, the PVR had fallen by a median 564 dyn*s*cm^{-5} (67.8%) from PPP (P=0.047). No difference was found between the groups after release of the gas from the abdominal cavity.

There was a strong correlation between PVR and the number of embolisms; Spearman's partial correlation, r=0.802, P=0.003 at AVC, and r=0.705, P=0.005 at PPP (Figure 38).

Gas exchange

$PaCO_2$

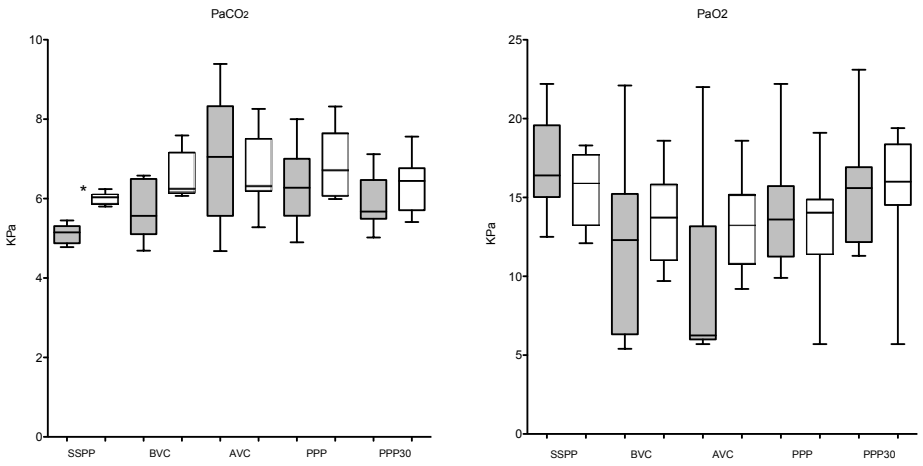

Figure 39. Box plot showing left, $PaCO_2$ and right, PaO_2. Clear boxes represent interquartile range in group-CO_2 and grey boxes group-Ar. Median is presented as a line and the whiskers represent the 10th and 90th percentiles. Significant differences between the groups are marked with. No difference was found in PaO_2 between the groups.*

The $PaCO_2$ was higher in group-CO_2 at steady state after established pneumoperitoneum. In the remaining measurement points, there was not a difference between the groups. In group-CO_2, the level of $PaCO_2$ increased by a median 0.23 KPa (3.8%, P=0.016) from SSPP to BVC and did not change until it fell by a median 0.27 KPa (4.0%, P=0.016) between the last two measurements in the experiment. In group-Ar, the rise happened between the BVC and AVC, during the resection where the $PaCO_2$ increased by median 1.48 KPa (26.6%, P=0.039). The $PaCO_2$ then decreased again between the AVC and PPP by a median 0.77 KPa (10.9%, P=0.039). There was a trend to further reduction in $PaCO_2$ between the last two measurements in group-Ar (P=0.055) (Figure 39).

PaO_2

The PaO_2 fell in both group-Ar and group-CO_2, between the steady state after established pneumoperitoneum to the measuring point before the vein

injury, by a median 4.1 KPa (25%, P=0.016) and 2.1 KPa (13.2%, P=0.031), respectively. There was trend toward a further fall in group-Ar during the resection, by 6.05 KPa (49.2%, P=0.078). The PaO_2 turned between AVC and PPP and increased by 7.35 KPa in group-Ar; however, it was unchanged in group-CO_2. A further rise in PaO_2 was seen between the last two measuring points in both groups; by a median 2.0 KPa in group-Ar (P=0.014) and a median 1.9 KPa in group-CO_2 (P=0.031). No significant differences were seen between the groups regarding PaO_2 (Figure 39 right).

End-tidal CO_2

When the steady state after established pneumoperitoneum was reached, there was a difference in end-tidal CO_2 between the groups. The difference was significant until the last measurement at the thirtieth minute after the release of IAP (P<0.032). The only change in the group-CO_2 was seen between the AVC and PPP where there was an increase in end-tidal CO_2 of median 0.1 KPa (P=0.049). On the other hand, in group-Ar, there were changes seen in end-tidal CO_2, with a decrease between SSPP and BVC and increase between AVC and PPP; median 1.3 KPa (25.7%, P=0.016) and 1.2 KPa (27.9%, P=0.008), respectively (Figure 40).

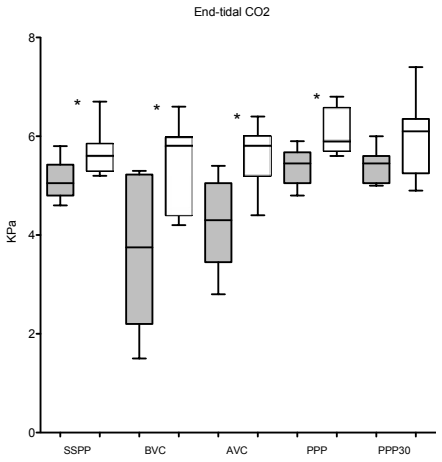

Figure 40. Box plot showing end-tidal CO_2. Clear boxes represent interquartile range in group-CO_2 and grey boxes group-Ar. Median is presented as a line and the whiskers represent the 10th and 90th percentiles. Significant differences between the groups are marked with.*

pH

There was a difference by 0.065 in pH between the groups in the beginning, at the steady state after established pneumoperitoneum (P=0.010). There was a trend towards difference at the first part of the operation, before the vein injury (P=0.058). There was a decrease in pH, resulting in acidosis in both groups between SSPP and BVC, by a median 0.068 (P=0.047) in group-Ar and a median 0.067 (P=0.022) in group-CO_2. A further reduction occurred by a median 0.010 between BVC and AVC in group-Ar (P=0.022). Between the last two measurements, there was a rise in pH in both groups (P<0.030).

Group-Ar did end above 7.40 in pH; however, group-CO_2 remained in acidosis with a median pH value of 7.39. There was a strong correlation between the decrease in pH and the number of embolisms in group-Ar; Spearman's partial correlation coefficient r≤-0.685 with P≤0.005 (Figure 41).

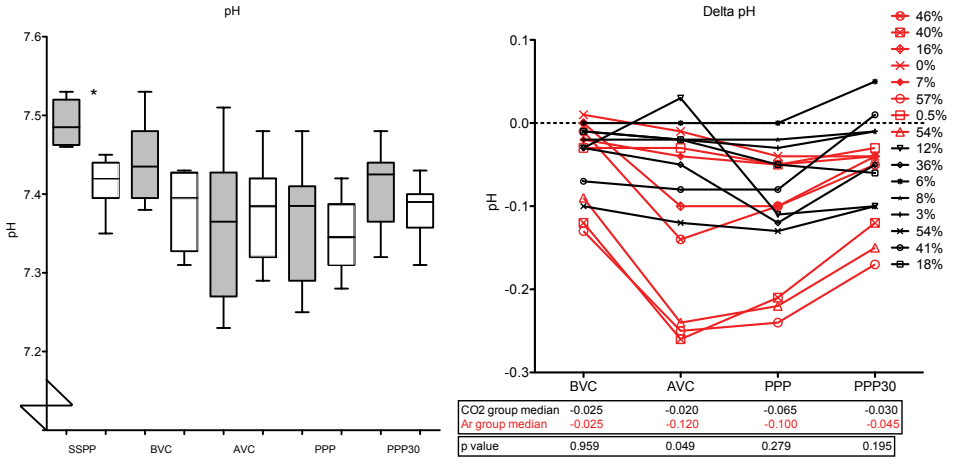

*Figure 41. Left: Box plot showing the pH. Clear boxes represent the interquartile range in group-CO_2 and the grey boxes in group-Ar. Median is presented as a line and the whiskers represent the 10th and 90th percentiles. Significant differences between the groups are marked with *. Right: delta pH is shown for each animal. Each red line represents one animal in group-Ar, and each black line represents an animal in group-CO_2. The total number of embolisms is shown in % of total operation time for each animal.*

Study IV

There was no significant variation between the groups in weight of animals, median 27.5 kg (22.5–28.1 kg) in group-L and 28.1 kg (23.5–33.0 kg) in group-S (P=0.270), or in weight of the removed liver, median 121.5 g (89–162 grams) in group-L and 115 g (88–161 g) in group-S (P=0.668).

Operating time

The use of staples for resection shortened the operation time by a median 7 min (42%, P=0.004). The operation time for group-L was a median 16.5 min (from 12 to 22 min) and for group-S, a median 9.5 min (from 6 to 19 min).

Bleeding

There was less bleeding in group-S, median 133.5 mL (range: 113-170 mL) compared to median 182.5 mL (range:113-448 mL) in group-L (P=0.021).

Embolism

All animals in group-L showed grade 1 embolisms during the operation; however, only two animals in group-S had grade 1 embolisms (P<0.001). These embolisms were of 6 s variation in one animal and 11 s in the other. Grade 2 embolisms were registered in one animal in group-L and none in group-S.
The length of embolisms in both groups as a percent of the total operation time is presented in Figure 42. The median length of grade 1 embolism in group-L was 10.4% (3.3–29.0%), and in group-S, it was 0% (0–3.1%) (P<0.001)

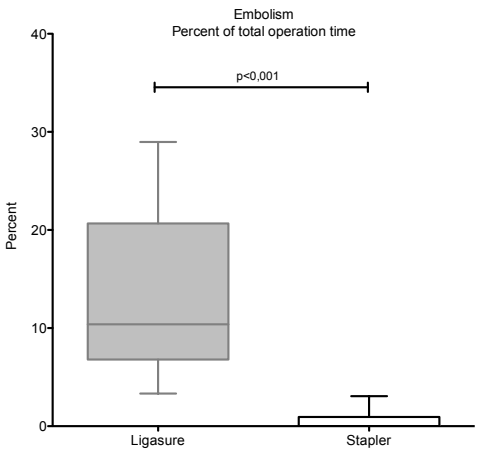

Figure 42. Box plot showing embolism as a percent of total operation time. Clear boxes represent interquartile range in group-S and grey boxes group-L. Median is presented as a line and the whiskers represent the 10th and 90th percentiles. A significant difference was calculated.

Gas exchange

$PaCO_2$

$PaCO_2$ was not different between the groups throughout the whole experiment (P>0.451). Both groups had increased $PaCO_2$ with introduction of CO_2 pneumoperitoneum; median 0.95 KPa in group-L and 0.85 KPa in group-S, P=0.013 and P=0.014, respectively. There was no change in $PaCO_2$ until after release of pneumoperitoneum when it decreased; however, at the end of the experiment, the level of $PaCO_2$ was still > 0.4 KPa higher than the baseline value (P<0.015) (Figure 43).

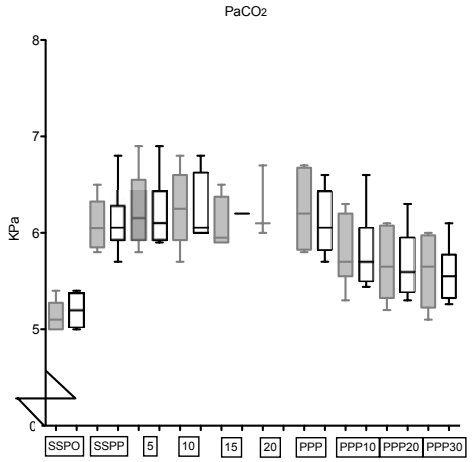

Figure 43. Box plot showing $PaCO_2$. Clear boxes represent interquartile range in group-S and grey boxes group-L. Median presented as a line and the whiskers represent the 10^{th} and 90^{th} percentiles. No differences were found between the groups.

PaO_2

As with $PaCO_2$, there were no differences in PaO_2 between the groups through the whole experiment (P>0.462). There was a trend for decrease in PaO_2 in group-S between SSPO and SSPP (P=0.078), or between SSPP and 5 min into the operation (P=0.055). However, in group-L, there was a significant fall at these time points, P=0.014 and P=0.039, respectively. Both groups had an increase in PaO_2 at the thirtieth minute after the release of pneumoperitoneum (P≤0.050). The PaO_2 had not reached the basic value in group-L at the end of the experiment (Figure 44).

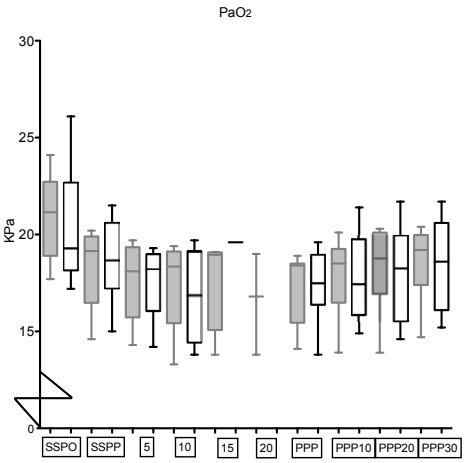

Figure 44. Box plot showing PaO_2. Clear boxes represent interquartile range in group-S and grey boxes group-L. Median is presented as a line and the whiskers represent the 10^{th} and 90^{th} percentiles. No differences were found between the groups.

End-tidal CO_2

The end-tidal CO_2 did not vary between the groups at any time during the whole experiment (P>0.166). There was increased end-tidal CO_2 at SSPP in both groups by a median 0.5 KPa (P<0.022). After SSPP, there was no change in the groups until after the release of gas from the abdominal cavity and in the following 30 min when the end-tidal CO_2 decreased and came down to baseline, pre-operative levels again (P>0.552) (Figure 45).

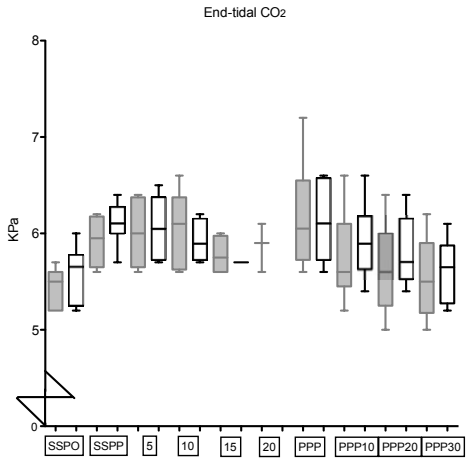

Figure 45. Box plot showing end-tidal CO_2. Clear boxes represent interquartile range in group-S and grey boxes group-L. Median is presented as a line and the whiskers represent the 10^{th} and 90^{th} percentiles. No differences were found between the groups.

pH

There was no difference between the groups throughout whole experiment (P>0.139).

A decrease in pH was seen after established pneumoperitoneum in both groups (P=0.001) by a median 0.080 in group-L and 0.075 in group-S. After that, there was no significant change within the groups or until the deflation of CO_2 from the abdominal cavity. At that point, there was an increase in pH that continued until the end of the experiment. The pH did not reach pre-operative values before the experiment was terminated in either group. Although the animals in both groups had decreased pH, the median value rarely fell below 7.40. However, there were some individual animals in both groups

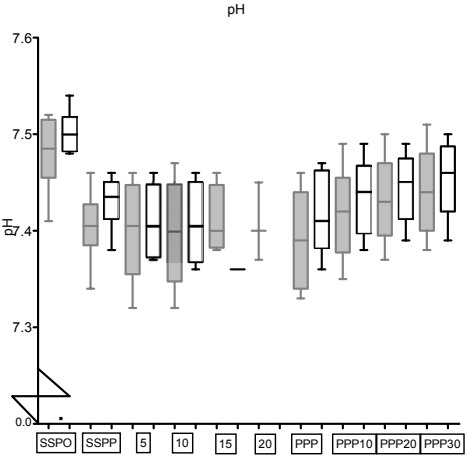

Figure 46. Box plot showing pH. Clear boxes represent interquartile range in group-S and grey boxes group-L. Median is presented as a line and the whiskers represent the 10^{th} and 90^{th} percentiles. No differences were found between the groups.

falling under 7.40 at some point. The lowest value in group-S was 7.34, and in group-L, it was 7.32 (Figure 46).

Systemic hemodynamics

Mean arterial pressure

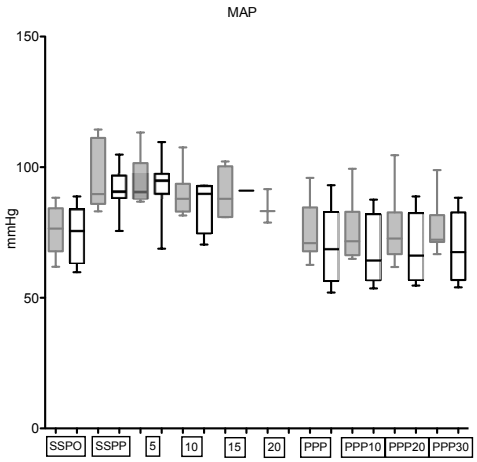

Figure 47. Box plot showing MAP. Clear boxes represent interquartile range in group-S and grey boxes group-L. Median is presented as a line and the whiskers represent the 10th and 90th percentiles. No differences were found between the groups.

No difference in MAP was found between the groups (P>0.195). There was an increase in MAP with the introduction of CO_2 to the peritoneal cavity in both groups. In group-L, this was detected as an increase by a median 13.2 mmHg (17.3%), and in Group-S, it was a rise by a median 15.2 mmHg (20.1%); P=0.008 for both groups. A trend was registered for a fall in MAP between the fifth and tenth minutes of the operation in group-L (P=0.055). For group-S, there was a slight increase in MAP between the tenth and twentieth minutes after release of the gas from peritoneum (P=0.023) (Figure 47).

Heart rate

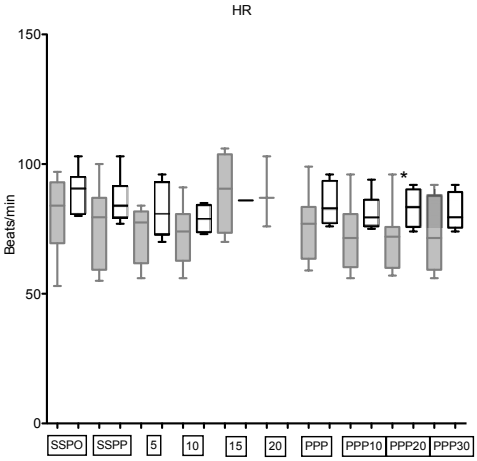

*Figure 48. Box plot showing HR. Clear boxes represent interquartile range in group-S and grey boxes group-L. Median is presented as a line and the whiskers represent the 10th and 90th percentiles. Differences between the groups are marked with *.*

At only one measuring point was there a statistical significant difference in HR between the groups and that was at the twentieth minute after release of the pneumoperitoneum (P=0.037). Group-S had a faster HR of 12 beats/min. The only change within the groups was registered in group-L between PPP and PPP10. There was a decrease in HR by 5 beats/min, from 77 to 72

beats/min (P=0.045). No variation was found in group-L between the HR at the beginning and the end of the experiment (P=0.146); however, in group-S, the difference was 11 beats/min (P=0.009) (Figure 48).

Central venous pressure

No difference in CVP was detected between the groups during the whole experiment (P>0.382). There was an increase in both groups with introduction of CO_2 to the abdominal cavity. In group-L, the CVP rose from a median 7 to 12 mmHg (71%) and in Group-S from 6 to 13 mmHg (116%); P<0.001 for both groups. The CVP fell after the release of IAP and in group-L returned to preoperative levels; however, in group-S, there was a difference of a median 1 mmHg (P=0.033) (Figure 49).

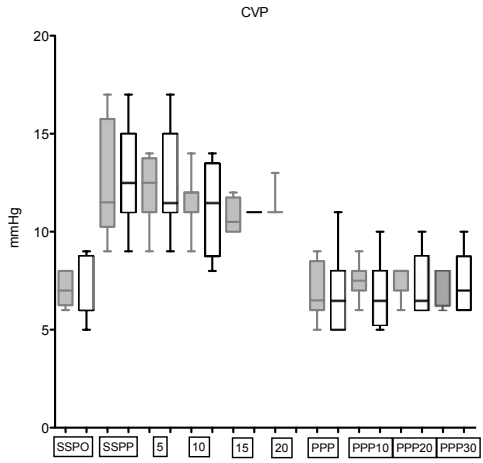

Figure 49. Box-plot showing CVP. Clear boxes represent interquartile range in group-S and grey boxes group-L. Median is presented as a line and the whiskers represent the 10th and 90th percentiles. No variation was registered between the groups.

Pulmonary hemodynamics

Mean pulmonary arterial pressure

MPAP did not differ between groups during the experiment (P>0.084). Values increased after the insufflation of CO_2 in the abdominal cavity in both groups. The increase was a median 7.1 mmHg in group-L and 5.1 mmHg in group-S, P<0.001 for both groups.

The animals in group-S then

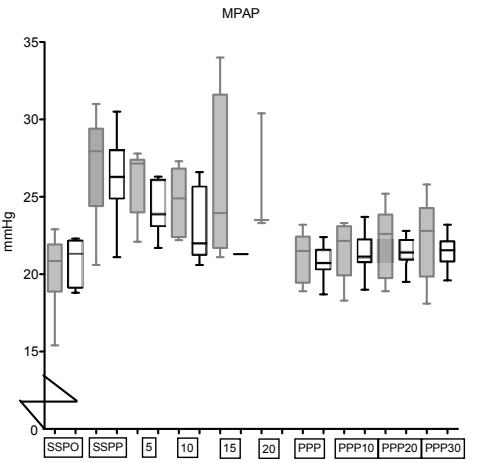

Figure 50. Box plot showing MPAP. Clear boxes represent interquartile range in group-S and grey boxes group-L. Median is presented as a line and the whiskers represent the 10th and 90th percentiles. No difference was registered between the groups.

showed a fall in MPAP during the first 5 min of the resection, by a median 2.5 mmHg (P=0.032). Within both groups, there was a gradual fall with a return to pre-operative levels at PPP (Figure 50).

Pulmonary vascular resistance

Ten minutes into the operations, there was a difference in PVR between the groups (P=0.033). This was the only measurable difference in PVR between the groups during the whole experiment. The difference was a median 144.1 dyn*s*cm^{-5}. No changes within the groups were great enough to give significant difference in PVR between the groups (P>0.061) (Figure 51).

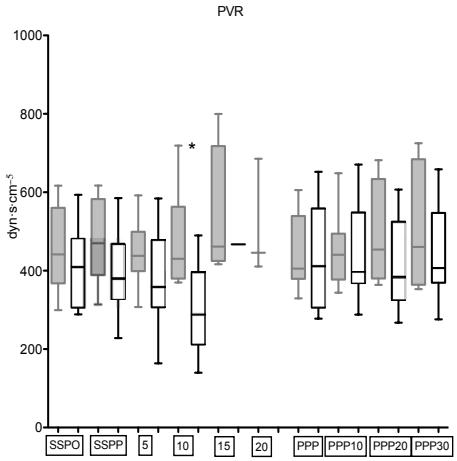

*Figure 51. Box plot showing PVR. Clear boxes represent interquartile range in group-S and grey boxes group-L. Median is presented as a line and the whiskers represent the 10th and 90th percentiles. Differences between the groups are marked with *.*

Discussion, findings, and implications

Study I

The aim of this study was to evaluate two transectional techniques of the liver with the endpoints of amount of bleeding and number of embolisms.
The main results from this study were that both combinations of Ligasure™/CUSA™ and Autosonix™/CUSA™ are safe to use for division of the liver parenchyma. No animal death was related to the choice of instruments. These instruments have been used in liver resections in humans and shown to be effective, without jeopardizing patient safety[4, 7, 31, 87, 96, 213-217].
There was more bleeding during the resection with UltraCision than with the vessel sealing system (P=0.020). Despite this difference, there were no more intra-operative problems in group-US.
A proposed reason for more bleeding in group-US is based on the different design of these instruments. The Ligasure™ is made as a U-shaped sealing contact; i.e., the sealing does work at the tip of the instrument as well, and the knife that divides the tissue after sealing does not extend to the tip of the instrument. If the surgeon has grasped a bigger vascular structure with the Ligasure™ without completely getting the vessel into the grasping capacity of the instrument, the described feature would close the remaining vessel in a way that would likely avoid bleeding. In contrast, in the same situation, the Autosonix™ would not seal the remaining vessel, with subsequent bleeding. It has to be stressed that bleeding from bigger vessels in the way described happened in both groups. When this occurred with Ligasure™ use, it was because the instrument stuck to the tissue after activation. Cleaning of the instrument prevented this problem.
The ergonomic qualities of the Autosonix™ were somewhat poorer than those of the Ligasure™, mainly because of the awkward design of the handle. Of course, this is a preference of each surgeon, and no study has been done to confirm this point of view. The correct use of these instruments is a major factor in obtaining the desired results. The surgeon's skill is a source of bias in this context.
Two observers independent of each other carried out the evaluation of the bleeding. In the published article, their agreement is presented as a correlation of their evaluation. This is not the correct way to present agreement and could not be corrected before the article was published. The correct way to establish the quality of agreement is by measuring the Cohen's kappa. In-

stead of measuring the degree to which two variables change together, as correlation does, the kappa measures the degree of actual agreement of these two variables. The kappa for the observers in this study was 0.68 (CI: 0.53–0.82), which is interpreted as good agreement. Calculating bleeding in a.u. as done in the published article is questionable method since the variable is strictly a categorical, ordinal type. By counting the observation the variable is changed to numerical, discrete and difference can be calculated. With this method the same results were found showing more bleeding in group-US.
There was a trend toward a shorter operating time (P=0.080) in group-VS that would be expected with less bleeding in that group because of presumably less time spent controlling bleeding and removing blood from the surgical field.
Our group has, with the same model, published a study comparing these instruments and others by performing smaller incisions that did not reach the bigger vessels in the liver[210]. These results did not show any differences between the instruments that were tested in our experiment regarding bleeding or operation time. However, contrary to the present study results, there was a longer total embolism time in the case of Ligasure™ compared to Autosonix™. Of interest, a clinical study of 50 patients randomized between open surgery with a clamp-crushing technique or CUSA™ revealed more air embolism during the use of CUSA™, 70% versus 100%, respectively[218].
In study I, there was a trend toward more grade 1 embolisms in group-US (P=0.080). No difference was found between the groups regarding grade 2 embolisms. This did not lead to any major intra-operative clinical problems compared to group-VS. A more thorough analysis of these same animals regarding embolisms has been published elsewhere, and the results showed hemodynamic and respiratory changes mainly during grade 2 embolisms[188].

With these findings, both the combination of CUSA™/Ligasure™ and CUSA™/Autosonix™ can be used safely during laparoscopic liver surgery. However, there was reduced bleeding during the use of the Ligasure™ combination and that has to be weighed in the process of choosing between these instruments. The following studies were conducted with the favorable combination found in this study.

Study II

This study was designed to evaluate the different effects of high and low IAP on bleeding and occurrence of embolism during LLR. The pressure level during LLR is variable among centers[5, 7, 10, 32]. Some authors have advocated

the use of high IAP (18 to 20 mmHg)[10] mainly to reduce bleeding. Animal studies have shown reduced bleeding with 15 mmHg IAP[122]. The value of 16 mmHg is just above the recommended maximum level of pneumoperitoneum for a general laparoscopic procedure and was the pressure of choice in group-H. The lowest pressure of CO_2 pneumoperitoneum during liver surgery reported is 8 mmHg[7] and that became the pressure of choice for group-L.

CO_2 is the gas of choice because it has relatively good solubility in blood[125]. Even so, there are reported fatal and near-fatal incidences of CO_2 embolisms[167, 169-173, 176, 185, 199].

The point of deliberate vein injury was to simulate a situation when accidental injury happens to a vein with special attention to the fact that during high pressure, it could take time to notice the damage. Three minutes were chosen for the vein to be held open, as an open vein that is partly withdrawn into the liver parenchyma by accidental division can be difficult to detect, and even more so if it does not bleed. The combination of CUSA™ and Ligasure™ was the technique of choice, demonstrated as more favorable in study I.

The primary endpoints of this study were the amount of bleeding and the number of embolisms. The outcome of these variables is of great interest for laparoscopic liver surgery because one of the major hazards during LLRs is bleeding. The fear of embolisms and a potential lethal outcome is evident[7, 10, 31, 32, 214], although few reports of clinically significant gas embolisms exist in connection with laparoscopic liver surgery[6, 49, 183-185].

More embolisms were observed with TEE in group-H, where all animals showed grade 1 embolisms (median 14.2% of operation time) and 5/8 grade 2 (median 2.3% of operation time). In group-L, only two animals had grade 1 embolism and only for a very short time. Most of the embolisms happened after division of the left vein, in accordance with findings by Schmandra et al[186] and in contrast to findings by Jayamara et al[219], who identified embolisms mainly during dissection around the big vein and occasionally during parenchymal division. The study by Schmandra et al[186] comparing an open (n=7) versus laparoscopic (n=7) approach in pigs showed embolisms (correlating to grade 1 in our study) in all seven animals in the laparoscopic group with an IAP of 12 mmHg. Four animals in the same study showed cardiac arrhythmias in contrast to our findings.

A good agreement was calculated between the observers that evaluated the bleeding from the operation recordings. The bleeding was reduced with high IAP (P=0.016). Most bleeding happened during the vein injury in both groups, although the bleeding was less in the high pressure group. The calculation of bleeding in a.u. as done in published article is questionable since the variables are strictly categorical, ordinal. By counting the observations the variables were converted to a numberical, discrete and could be used to calculate the difference between the groups. The same results were found

with significant higher number of observed grade 1 and 2 bleeding in group-L and significant less grade 0 observations in the same group.

The changes in hemodynamic parameters within group-L reflected the effects of hypovolemia, with lowering of MAP and lowering of CO, although the differences were not significant between the two groups. The CVP also decreased, and all these parameters were lower than the pre-operative values at the end of the experiment in group-L. The same effect was seen on the pulmonary circulation in that group. Surprisingly, there was no increase in HR. HR in group-H was unchanged as well, and there was no variation between the groups. Changes in HR by CO_2 pneumoperitoneum have been variable and contradictory between studies although many results are in agreement with ours and report no change[101, 104, 105, 107, 128, 130-132, 205]. No cardiac arrhythmias were detected. Tachycardia and bradycardia have been reported by others[117, 129, 133, 188]. The CVP was higher in group-H, as expected from a higher IAP pressure. The CVP changed in the same way as in group-L; however, unlike group-L, it was back to pre-operative values at the last measurement of the experiment. By analyzing the IAP–CVP gradient in our animals, most of the time we found a positive difference between IAP and CVP_{mean} both in animals that had embolism and those that did not. The main difference was that the animals in group-H had a steeper gradient of 5–8 mmHg compared to 0–3 mmHg in group-L. We identified a negative IAP–CVP_{mean} gradient in an animal that had embolism in group-L and a >10 mmHg gradient in animals that had a limited number of embolisms in group-H. Hence, the occurrence of embolisms in the presence of an open liver vein depended on more than just a negative IAP–CVP gradient. Jayamara et al[219] studied three groups of pigs through left hepatectomy with different IAP–CVP gradients and found no difference between the groups regarding number of embolisms. A question has been raised about the role of other physical components like the Venturi effect; however, this issue was not addressed in the current study.

The MAP increased with the introduction of raised IAP as has been shown by some other authors[101, 104, 105, 107, 126, 128, 130-132, 205, 220]. The CO did not change at all in group-H. With no change in CO and HR, we can estimate that SV was not changed because CO=SV*HR. The change in MAP then has to be the result of the increase in the SVR because MAP=SV·HR·SVR.

MAP changes in group-H were too weak to lead to a significant difference between the groups. Mayer et al[221] found a dose-dependent relationship between the number of embolisms and the change in MAP, where an embolus of 0.3 mL/kg·min led to an increase, 0.75 mL/kg·min did not have any effect, and an embolus of 1.2 mL/kg·min led to a decrease in MAP. They also found an increase in MPAP in all three groups.

Many authors have shown MPAP to rise with CO_2 pneumoperitoneum of 7–16 mmHg pressure[102, 104, 105, 107, 117, 126, 129-133, 188, 222]. In the present study, the MPAP rose after establishing the pneumoperitoneum in group-H (P=0.008), and there was also a trend to an increase in group-L (P=0.055). The groups

differed significantly during the first part of the operation, and there was a correlation between the number of embolisms and the rise in MPAP (Figure 37). The gas embolisms probably formed a "gas lock" in the circulation, thus diminishing capacity and increasing pressure in the circulation. Enough volume can lead to obstruction of right ventricular outflow. One possible explanation of this rise in MPAP could be a vasoconstrictive response to hypoxemia[223]. There was a trend to an increase in PVR after pneumoperitoneum was established and again at AVC in group-H.

Other studies have shown that the $PaCO_2$ increases with CO_2 pneumoperitoneum[101, 104, 106, 107, 117, 119, 126-129, 131, 132, 188, 205, 220]. The same happened in both groups, with more effect in the high pressure group. During the resection, the $PaCO_2$ in group-H increased even more, and there was significant variation between the groups right from the first measurement (BVC). The groups differed even after the release of IAP and at the last measurement in the experiment, indicating persistent disturbances of gas exchange in group-H. No such disturbances were noted in group-L. With the rise in $PaCO_2$, there was a decrease in PaO_2, as has been reported previously[101, 104, 105, 131, 188], although the difference between the groups was not significant until after the release of the pneumoperitoneum.

A decrease in pH was followed by acidosis in group-H, but the median value in group-L did not fall under normal values for a pig (7.40–7.53)[224]. Both lower pH and hypercapnia influence the oxygen–hemoglobin dissociation curve by shifting it to the right, i.e., lowering the affinity for O_2. [223]

The end-tidal CO_2 was not different between the groups. Because end-tidal CO_2 changes are rapid and last for a short period[188, 221] and measurements by our method were pre-fixed during the experiment, a change in end-tidal CO_2 could easily be missed in connection with the embolisms. There was a difference between end-tidal CO_2 after release of the pneumoperitoneum, with an increase in animals in group-H. With the constant high $PaCO_2$ in group-H, a high end-tidal CO_2 would also be expected; however, the effect of embolism with reduction in end-tidal CO_2[221, 225] could explain why there was not a difference between the two groups during resection. At BVC, there was a great variation in group-H because of three animals that experienced decreased end-tidal CO_2. These same animals showed the highest number of embolisms.

Mayer et al[221] studied effects of different amounts of continuous injection of CO_2 in 15 pigs. They found a sudden fall in end-tidal CO_2 at the start of infusion of the CO_2 embolus and a rise after that. No pattern of changes in end-tidal CO_2 was found that would be helpful for detecting fatal embolisms in the animals that died.

Standard monitoring during LLR is typically focused on the systemic circulation (AP, CVP, pulse rate) in combination with end-tidal CO_2 measurement. Although such measurements are usually sufficient to evaluate bleeding, gas embolism does not affect these parameters until very late. An initial decrease in the pulmonary gas exchange decreases the end-tidal CO_2. During

a later phase, CO_2 accumulation in the blood increases $PaCO_2$, and eventually end-tidal CO_2 also rises. These changes can be very rapid, and only very close monitoring will detect ongoing embolism, making end-tidal CO_2 an unreliable method for detection of gas embolism. Online blood gas measurements may be the best monitoring strategy because these measurements immediately identify clinically significant gas at a stage when necessary steps (lowering IAP, identification of open venous vessels) can be taken.
Higher IAP does lead to less bleeding but with an increase in gas embolisms although none of these had a devastating outcome on the healthy animals in this study.

Study III

This study was designed to compare the effects of Ar and CO_2 embolisms on gas exchange and circulation during experimental LLR. With Ar pneumoperitoneum instead of Ar beamer, the danger of Ar embolism could be studied without the disturbance of the somewhat unstable flow of the Ar beamer. The same setup of the animal model as in study II was used, with 16 mmHg pressure in the abdomen in both groups but Ar instead of CO_2 in one group.
Argon enhanced coagulation (AEC) is a well-known method to acquire hemostasis during liver surgery. The Ar gas carries the electric charge to the tissue, resulting in a coagulating effect to the surface. The safety of AEC has been discussed[226], and by using the AEC during laparoscopic surgery, a hazardous situation can arise with increased risk of Ar embolisms[227]. There have been near-fatal and fatal outcomes reported from Ar embolisms in this way[168, 199, 201, 202, 228-231]. The danger of Ar "pushing" out or replacing the CO_2 has been addressed[202]. The increased pressure of Ar turns off the automatic flow of the insufflator, and no CO_2 is added to the abdominal cavity. This would then lead to pneumoperitoneum mainly of Ar gas and the possibility of higher IAP than the cut-off value of the insufflator[226]. Even so, not all surgeons have abandoned the use of Ar and still advocate cautious use during LLR[232, 233]. The presented model could be assessed as somewhat extreme because Ar would probably not reach 100% in the clinical circumstances used in this study; however, there was not the possibility of measuring the amount of Ar in the abdomen or for that matter surrounding the liver surface during clinical use of AEC. The stream of Ar from the AEC can, per se, lead to Ar embolism if used on an open vessel.

The number of embolisms was the same in both groups during the experiment (P=0.879). Although there was not a major focus on the bleeding in this study, we had to ensure no differences between the bleeding in the groups because that could influence the results of hemodynamic measurements. Blood and fluid measured from the suction of CUSA™ and from the abdomen after the experiment composed the total bleeding in each animal. No differences were found in bleeding (P=0.500). The possible bias with regard to excess fluid in some of the animals' abdomens is recognized.

The groups did not differ in MAP except at AVC where group-Ar had a fall of a median 20.3 mmHg. With that, the HR increased in group-Ar between BVC and AVC, as expected, but there still were no differences between the groups regarding HR. The calculated SVR showed a trend (P=0.071) toward a fall in group-Ar during the resection. CO decreased in group-Ar during the resection (P=0.028), indicating that the MAP fell because of a fall in stroke volume. The HR increased, the SVR decreased and MAP decreased during the resection in group-Ar; thus, since MAP=SV·HR·SVR there must be some decrease in the SV. This decrease was confirmed with measurements in which SV did differ between the groups between BVC and AVC. Eisenhauer et al[136] have described a 25% fall in SVI (SVI=CO/HR/weight in kg) during Ar pneumoperitoneum. They also showed an increase in SVR, in contrast to the present findings.

The CVP was higher in group-Ar at AVC and again at the last measuring point in the experiment. Both groups showed steady CVP during the resection and had a decrease, as expected, with the release of pneumoperitoneum.

There was higher MPAP in group-Ar at AVC (P=0.050) and a correlation between the number of embolisms and the rise in MPAP at AVC. A similar change was seen in PVR with variation between the groups at AVC and a strong correlation between embolism and increase in PVR. These changes were more prominent in group-Ar and can partly be explained from longer lasting effects of blockage by Ar in the pulmonary circulation and a possible increase of neural, neurohumoral, cellular, and humoral vasoactive mediators influencing PVR and thus PAP. No change was observed in PVR in group-CO_2, although increased resistance during CO_2 embolism has been previously described[225].

Mann et al[234] also found no difference in PAP and MAP between Ar and CO_2 pneumoperitoneum. Results from the embolism part of their study were in agreement with the changes identified in the current work in PAP and MAP between Ar and CO_2 embolism with emboli sizes at 0.4 mL/kg and 2.0 mL/kg, respectively. These same changes were also confirmed by Junghans et al[235].

$PaCO_2$ was higher in group-CO_2 at steady state after established pneumoperitoneum, as would be expected because of diffusion of CO_2 from the peritoneum to the blood circulation[234]. There was an increase in both groups during the resection with the highest value at AVC when most of the

embolisms happened; however, there was no variation between the groups. PaO_2 fell in both groups and returned to baseline levels at the end of the observation time. No differences were observed between the groups regarding PaO_2. The end-tidal CO_2 was higher in group-CO_2, as expected from the diffusion of CO_2. During the operation, the end-tidal CO_2 fell in group-Ar, reflecting the effect of Ar embolism on gas exchange.
After established pneumoperitoneum, the groups differed in pH as a reflection of high $PaCO_2$. During the operation, group-Ar showed a decrease, but the groups did not differ through the remainder of the experiment. This fall in the Ar group was the result of embolisms, and there was a strong correlation between the number of embolisms and a fall in pH.
The solubility of Ar in blood (Ostwald's solubility: 0.0281 mL/mL human plasma) is less than CO_2 (0.582 mL/mL human plasma)[125]; therefore, more profound and sustained effects are expected to occur with the same amount of gas embolism when comparing Ar versus CO_2 embolism, providing the likely physiological explanation for the results obtained in our study. Although we eliminated the direct flow of Ar into the liver tissue, the replacing of CO_2 with Ar gas in the abdomen caused serious changes when gas embolism occurred although not leading to death in any of the healthy animals operated on in this study.
If Ar gas is used, great care is necessary along with careful monitoring of the patient during LLR.

Study IV

Two techniques for division of the liver parenchyma have been tested in this study. This animal study was design to evaluate the bleeding and number of potential embolisms during left lateral liver resection, by staple technique (Endo-GIA™) versus Ligasure™ and CUSA™.
The staple device has been used within the disciplines of gastrointestinal surgery for 100 years[236]. In the last two decades, the staple instrument has become readily available and user friendly. The use in hepatic surgery was mainly for securing the vascular closure[237-246] or resection of cysts[245, 247]; however, reports are now emerging including the use of the staple device as an aid to transect the liver[92, 248-251]. With the use of staples, one can expect closure of all luminous structures, thereby reducing the bleeding, bile leakage, and possible gas embolisms.
There was a 42% shorter operating time with the staple device technique (P=0.004). There was more bleeding documented after resection with Ligasure™ and CUSA™.

The porcine liver is thinner than the human liver, with a maximum thickness of 3 cm in the chosen line of resection. As observed earlier, the staple can manage a human liver of 2.5 cm thickness[250]. There was an obvious crushing effect of the stapler at times that did introduce bleeding. When crushing happens, it leaves a part of the resection line outside the staple edge and thus invites bleeding and possible gas embolisms through these unclosed vascular structures. The technique for using the staple device in a thick human liver is to divide the parenchyma down to the bigger structures with another instrument and then use the staple on the larger vasculature. Tunneling is not recommended because it can lead to uncontrollable bleeding[252, 253].

Group-L had more embolisms ($P<0.001$). The median length of grade 1 embolisms in this group was 10.4% (3.3–29.0%) of the operation time versus median 0% (0–3.1%) in Group-S. All animals in group-L had embolism and two in group-S did. We are not aware of any other study that has been conducted to look at embolisms in the context of the staple technique. There is one survival animal study on a porcine model that examined the efficacy of the staple device for division in LLR. The endpoints in that study were operating time, bleeding, and bile leakage intra-operatively and post-operatively[254]. The authors found similar results in the groups regarding endpoints although there was a trend towards more bleeding in the staple group, in contrast to our findings. An experimental study suggested the use of bioabsorbable reinforcement with stapling that resulted in less biliary leakage and less bleeding[255]. Another experimental study was published earlier in which open resection of the left liver lobe was undertaken with either the "finger fracture" technique or staples[256]. No difference was found between the two techniques regarding operation time or bleeding. A time-sparing effect of the staple technique has reported in a clinical trial where the warm ischemic time was also reduced[248]. A longer operation time and more bleeding are related to poorer outcomes[257, 258].

The rise in MPAP has been a good indicator of gas embolism. There was just a trend towards a rise in MPAP, in group-L, at the fifth minute in the operation ($P=0.084$); however, the groups differed regarding PVR at the tenth minute, which can represent an effect of the embolisms in group-L. Our group previously showed that grade 2 embolisms are what is mainly reflected in a change of these parameters[188]. In the current study, the embolism was not sufficient to elicit considerable changes in the pulmonary hemodynamics. No inter-group differences were recorded in the systemic hemodynamics or in the gas exchange. The previously described effects of CO_2 pneumoperitoneum were seen in both groups.

We found advantages in using the staple device in terms of reducing the operating time, bleeding, and gas embolisms during LLR. An appropriate thickness of liver has to be chosen if the staple device is to include all structures and prevent crushing of the tissue.

Conclusions

Both combinations of CUSA™/Ligasure™ and CUSA™/Autosonix™ can be used for laparoscopic liver resection. Intraoperative bleeding is less with the CUSA/Ligasure combination. Parenchymal stapling reduces operating time, bleeding, and gas embolism during LLR compared to the combination of CUSA™/Ligasure™.

Higher intraabdominal pressure reduces bleeding but with an increased risk for gas embolism during LLR. Standard intraoperative monitoring is generally focused on systemic hemodynamics, peripheral oxygenation and end-tidal CO_2 measurements. Online blood gas measurements and TEE are more sensitive for early detection of gas embolism.

Argon gas embolism causes more disturbances of the pulmonary circulation and gas exchange in comparison to CO_2 gas embolism. It is doubtful if Argon gas should be used during LLR, and if so, careful monitoring of the patient is necessary.

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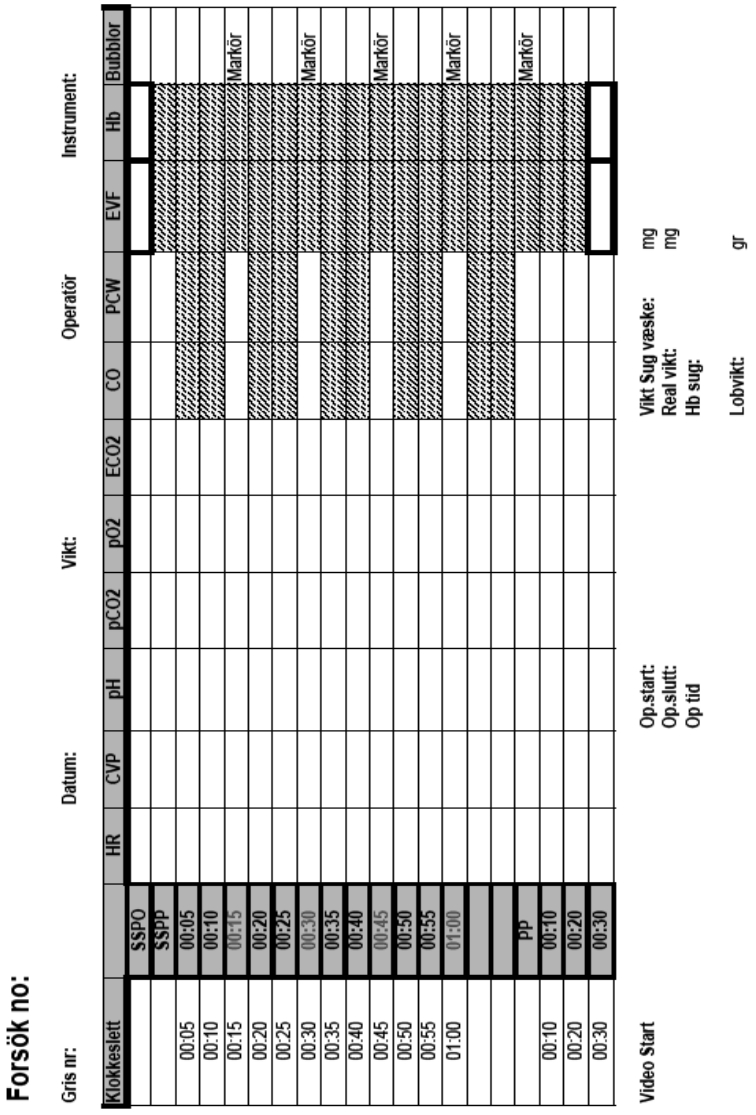
Appendix A.

Effect of pneumoperitoneum on systemic hemodynamic shown in other studies.
The table shows how the hemodynamic variables change with pneumoperitoneum; (↑): increase, (↓): decrease, and (↔): no change.

Author	PP (mmHg)	n	Subjects	MAP	CVP	HR	CO
Volpino et al[101]	12-15	120	Human	-	-	↔	-
Richard et al [205]	12	20	Pigs	↑	-	↔	↔
Lister et al[128]	15	12	Pigs	↑	-	↔	↔
Ho et al[126]	15	8	Pigs	↑	-	-	↔
Ho et al [259]	15	8	Pigs	↑	↑	↑	↔
Junghans et al[117]	16	18	Pigs	↑	↑	↑	↓
Horvath et al[107]	15	24	Pigs	↔	↑	↔	↑
Myre et al[132]	15	11	Human	↑	-	↔	↔
Myre et al[133]	15	8	Pigs	↑	-	↓	↔
Bannenberg et al[130]	15	8	Pigs	↑	-	↔	↑
Anderson et al[129]	11-13	8	Human	↑	↑	↑	↔
Fors et al[188]	16	15	Pigs	↑	↑	↓	↔
Windberger et al[104]	14	10	Pigs	↔	-	↔	↔
Shuto et al[119]	16	16	Pigs	↔	-	-	↓
Windberger et al[106]	12	9	Pigs	↑	-	↓	-
Rademaker et al[105]	15	8	Pigs	↑	↑	↔	↔
Hung et al[220]	15	8	Pigs	↑	-	-	↔
Rasmussen et al[222]	15	11	Pigs	↑	↑	-	↓
McDermott et al[131]	12	12	Pigs	↑	-	↔	↔
McLaughlin et al[260]	15	18	Human	↑	↑	-	↓
Volz et al[261]	14 (18)	6(5)	Pigs	↑(↑)	↑(↑)	↔	↔

Appendix B.

Registration form.



Forsök no:

Gris nr: Datum: Vikt: Operatör Instrument:

Klokkeslett		HR	CVP	pH	pCO2	pO2	ECO2	CO	PCW	EVF	Hb	Bubblor
	SSPO											
	SSPP											
00:05	00:05											
00:10	00:10											
00:15	00:15											Markör
00:20	00:20											
00:25	00:25											
00:30	00:30											Markör
00:35	00:35											
00:40	00:40											Markör
00:45	00:45											
00:50	00:50											
00:55	00:55											Markör
01:00	01:00											
	PP											Markör
00:10	00:10											
00:20	00:20											
00:30	00:30											

Video Start

Op.start:
Op.slutt:
Op tid

Vikt Sug væske: mg
Real vikt: mg
Hb sug:

Lobvikt: gr

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